

R	ID NO. 8485 as residues: Thr-5 to Val-10.
HWMCI32 R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 8498 as residues: Lys-5 to Glu-12.
HWMCL55 R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 8521 as residues: Pro-3 to Asn-8.
HWMCM32 R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 8528 as residues: Ser-9 to Thr-16.
HWMCM80 R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 8534 as residues: Pro-2 to Ala-8.
H2CBK69R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 8540 as residues: Thr-1 to Ile-6, Gly-35 to Ser-42, Ile-68 to Arg-76.
H2CBD14R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 8541 as residues: Asp-57 to Leu-62.
HDTEO77R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 8547 as residues: Glu-9 to Gly-17.
HCRNC15R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 8548 as residues: Asp-26 to Gln-33, Leu-61 to Cys-66, Thr-143 to Asp-155.
HWLRD05 R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 8549 as residues: Glu-108 to Asp-119.
HPWBS43R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 8550 as residues: Thr-8 to Ala-14.
H2CBU94R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 8551 as residues: Gln-7 to Lys-15, Cys-23 to Tyr-31, His-40 to Glu-47, Arg-66 to Cys-79, Lys-91 to Arg-98.
HWMCC56 R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 8554 as residues: Pro-30 to Ser-35, Arg-37 to Cys-42, Pro-47 to Gly-53, Arg-61 to Gln-66.

The present application is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the polypeptide sequence set forth. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Preferably, the polynucleotide fragments of the invention encode a polypeptide which demonstrates a functional activity. By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to a cancer specific polypeptide), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

The functional activity of the colon and/or colon cancer related polypeptides, and fragments, variants derivatives, and analogs thereof, can be assayed by various methods.

For example, in one embodiment where one is assaying for the ability to bind or compete with full-length polypeptide of the present invention for binding to anti-polypeptide antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.



In another embodiment, where a ligand is identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky, E., et al., 1995, Microbiol. Rev. 59:94-123. In another embodiment, physiological correlates polypeptide of the present invention binding to its substrates (signal transduction) can be assayed.

In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the present invention and fragments, variants derivatives and analogs thereof to elicit polypeptide related biological activity (either in vitro or in vivo). Other methods will be known to the skilled artisan and are within the scope of the invention.

Among the especially preferred fragments of the invention are fragments characterized by structural or functional attributes of polypeptides of the present invention. Such fragments include amino acid residues that comprise alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet-forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, surface forming regions, and high antigenic index regions (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) of complete (i.e., full-length) SEQ ID NO:Y. Certain preferred regions include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence, such preferred regions include; Garnier-Robson predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Kyte-Doolittle predicted hydrophilic and hydrophobic regions; Eisenberg alpha and beta amphipathic regions; Emini surface-forming regions; and Jameson-Wolf high antigenic index regions, as predicted using the default parameters of these predictive algorithms. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In additional embodiments, the polynucleotides of the invention encode functional attributes of the polypeptides of the present invention. Preferred embodiments of the

invention in this regard include fragments that comprise alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions of polypeptides of the present invention. Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotide fragments encoding these domains are also contemplated.

Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

### **Epitopes & Antibodies**

The present invention encompasses colon and/or colon cancer related polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:Y, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in a clone deposited with the ATCC or encoded by a polynucleotide that hybridizes to the complement of the sequence of SEQ ID NO:Y or contained in a deposited clone under stringent hybridization conditions or lower stringency hybridization conditions as defined supra.

The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X) polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand under stringent hybridization conditions or lower stringency hybridization conditions defined supra.

The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an

antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described infra. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985), further described in U.S. Patent No. 4,631,211).

In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

Non-limiting examples of antigenic polypeptides or peptides that can be used to generate colon cancer antigen-specific antibodies include a polypeptide comprising the portion(s) of SEQ ID NO:Y specified in Table 8. These polypeptide fragments have been determined to bear antigenic epitopes of the colon and/or colon cancer related proteins of the invention by the analysis of the Jameson-Wolf antigenic index which is included in the DNASTar suite of computer programs. Thus, an antigenic portion of a colon and/or colon cancer related polypeptide of the invention may comprise the portion of SEQ ID NO:Y shown in Table 8 or may comprise the portion shown in Table 8. By "comprise" it is

intended that an antigenic polypeptide may contain the portion of the polypeptide shown in Table 8 but it may contain additional flanking residues on either the amino or carboxyl termini of the recited portion. Such additional flanking sequences are preferably sequences naturally found adjacent to the portion; i.e., contiguous sequence shown in SEQ ID NO:Y.

5 Said flanking sequence may, however, be sequences from a heterologous polypeptide, such as from another colon and/or colon cancer related protein described herein or from a heterologous polypeptide not described herein.

Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson  
10 et al., supra; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein,  
15 such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

20 Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, in vivo immunization, in vitro immunization, and phage display methods. See, e.g., Sutcliffe et al., supra; Wilson et al., supra, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If in vivo immunization is used, animals may be immunized with free peptide; however, anti-peptide  
25 antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice  
30 are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 µg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune

response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide  
5 antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention comprising an immunogenic or antigenic epitope can be fused to other polypeptide sequences. For example, the polypeptides of the present invention may be fused  
10 with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof), or albumin (including but not limited to recombinant albumin (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. Such fusion  
15 proteins may facilitate purification and may increase half-life in vivo. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., Nature, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been  
20 demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., J.  
25 Biochem., 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, Proc. Natl. Acad. Sci.  
30 USA 88:8972- 897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix

binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni<sup>2+</sup> nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of polypeptides corresponding to SEQ ID NO:Y, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., Curr. Opin. Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety).

In one embodiment, alteration of polynucleotides corresponding to SEQ ID NO:X and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

## 25 Antibodies

Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of SEQ ID NO:Y, and/or an epitope, of the present invention (as determined by immunoassays well known in the art for assaying specific antibody-antigen binding). Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies

(including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In preferred embodiments, the immunoglobulin molecules of the invention are IgG1. In other preferred embodiments, the immunoglobulin molecules of the invention are IgG4.

Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')<sub>2</sub>, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, sheep rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, by size in contiguous amino acid residues, or listed in the Tables and Figures. Preferred epitopes of the invention include those shown in Table 8, as well as polynucleotides that encode these epitopes. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, or  $10^{-15}$  M.



The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described supra). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using

methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., *Blood* 92(6):1981-1988 (1998); Chen et al., *Cancer Res.* 58(16):3668-3678 (1998); Harrop et al., *J. Immunol.* 161(4):1786-1794 (1998); Zhu et al., *Cancer Res.* 58(15):3209-3214 (1998); Yoon et al., *J. Immunol.* 160(7):3170-3179 (1998);  
5 Prat et al., *J. Cell. Sci.* 111(Pt2):237-247 (1998); Pitard et al., *J. Immunol. Methods* 205(2):177-190 (1997); Liautard et al., *Cytokine* 9(4):233-241 (1997); Carlson et al., *J. Biol. Chem.* 272(17):11295-11301 (1997); Taryman et al., *Neuron* 14(4):755-762 (1995); Muller et al., *Structure* 6(9):1153-1167 (1998); Bartunek et al., *Cytokine* 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

10       Antibodies of the present invention may be used, for example, but not limited to, to purify, detect, and target the polypeptides of the present invention, including both in vitro and in vivo diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g., Harlow et al., *Antibodies: A Laboratory*  
15 *Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically  
20 conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

25       The antibodies of the invention include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by  
30 known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation,

metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of-interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples. In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then

assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')<sub>2</sub> fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). F(ab')<sub>2</sub> fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., J. Immunol. Methods 182:41-50 (1995); Ames et al., J. Immunol. Methods 184:177-186 (1995); Kettleborough et al., Eur. J. Immunol. 24:952-958 (1994); Persic et al., Gene 187 9-18 (1997); Burton et al., Advances in Immunology 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908;

5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')<sub>2</sub> fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., *BioTechniques* 12(6):864-869 (1992); and Sawai et al., *AJRI* 34:26-34 (1995); and Better et al., *Science* 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., *Methods in Enzymology* 203:46-88 (1991); Shu et al., *PNAS* 90:7995-7999 (1993); and Skerra et al., *Science* 240:1038-1040 (1988). For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Gillies et al., (1989) *J. Immunol. Methods* 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al.,

Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically

useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, Int. Rev. Immunol. 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., Bio/technology 12:899-903 (1988)).

Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" polypeptides of the invention using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, FASEB J. 7(5):437-444; (1989) and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand. For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligands/receptors, and thereby block its biological activity.

### ***Polynucleotides Encoding Antibodies***

The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or lower stringency hybridization conditions, e.g., as defined supra, to polynucleotides that encode an antibody, preferably, that

specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y.

The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., *BioTechniques* 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, *Molecular Cloning, A Laboratory Manual*, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.



In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well known in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described supra. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed supra, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described supra, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423-42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single

chain polypeptide. Techniques for the assembly of functional Fv fragments in *E. coli* may also be used (Skerra et al., Science 242:1038- 1041 (1988)).

### ***Methods of Producing Antibodies***

5           The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain  
10   antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology  
15   using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA  
20   techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT  
25   Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an  
30   antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains

may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., *Gene* 45:101 (1986); Cockett et al., *Bio/Technology* 8:2 (1990)).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther et al., *EMBO J.* 2:1791 (1983)), in which the antibody coding sequence may be ligated

individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein

products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, 5 eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for 10 example, CRL7030 and Hs578Bst.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control 15 elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their 20 chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

A number of selection systems may be used, including but not limited to the herpes 25 simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgprt- or aprt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to 30 methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers

resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, 1993, TIB TECH 11(5):155-215); and hygromycin, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by

chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either in vitro or in vivo, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., supra, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452(1991), which are incorporated by reference in their entireties.

The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851;

5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337-11341(1992) (said references incorporated by reference in their entireties).

5 As discussed, supra, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the in vivo half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported  
10 example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP 394,827; Traunecker et al., Nature 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having disulfide- linked dimeric structures (due to the IgG) may also be more efficient in binding  
15 and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995)). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP A 232,262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For  
20 example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., J. Molecular Recognition 8:52-58 (1995); Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).

25 Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA  
30 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the



“HA” tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the “flag” tag.

The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include <sup>125</sup>I, <sup>131</sup>I, <sup>111</sup>In or <sup>99</sup>Tc.

Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytotoxic agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, <sup>213</sup>Bi. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g.,

mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor,  $\alpha$ -interferon,  $\beta$ -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF- $\alpha$ , TNF- $\beta$ , AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti- angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of

Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62:119-58 (1982).

5           Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

          An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a  
10   therapeutic.

### ***Immunophenotyping***

          The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. The translation product of the gene of the present invention may be  
15   useful as a cell specific marker, or more specifically as a cellular marker that is differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the  
20   marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al.*, *Cell*, 96:737-49 (1999)).

          These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in  
25   acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

### ***Assays For Antibody Binding***

          The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited

to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X- 100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or

alkaline phosphatase) or radioactive molecule (e.g.,  $^{32}\text{P}$  or  $^{125}\text{I}$ ) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g.,  $^3\text{H}$  or  $^{125}\text{I}$ ) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g.,  $^3\text{H}$  or  $^{125}\text{I}$ ) in the presence of increasing amounts of an unlabeled second antibody.

### *Therapeutic Uses*

The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, 5 antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, 10 including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable 15 compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are 20 described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth 25 factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species 30 origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments

derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, and  $10^{-15}$  M.

### *Gene Therapy*

In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., *Clinical Pharmacy* 12:488-505 (1993); Wu and Wu, *Biotherapy* 3:87-95 (1991); Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 260:926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62:191-217 (1993); May, *TIBTECH* 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); and Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990).

In a preferred aspect, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the

antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

In a specific embodiment, the nucleic acid sequences are directly administered in vivo, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635;



WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)).

5 In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy  
10 are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., Biotherapy 6:291-302 (1994), which describes the use of a retroviral vector to deliver the mdrl gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., J.  
15 Clin. Invest. 93:644-651 (1994); Kiem et al., Blood 83:1467-1473 (1994); Salmons and Gunzberg, Human Gene Therapy 4:129-141 (1993); and Grossman and Wilson, Curr. Opin. in Genetics and Devel. 3:110-114 (1993).

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses  
20 naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, Current Opinion in Genetics and Development 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., Human Gene  
25 Therapy 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., Science 252:431-434 (1991); Rosenfeld et al., Cell 68:143- 155 (1992); Mastrangeli et al., J. Clin. Invest. 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., Gene Therapy 2:775-783 (1995). In a preferred  
30 embodiment, adenovirus vectors are used.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., Proc. Soc. Exp. Biol. Med. 204:289-300 (1993); U.S. Patent No. 5,436,146).

Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, *Meth. Enzymol.* 217:599-618 (1993); Cohen et al., *Meth. Enzymol.* 217:618-644 (1993); Cline, *Pharmac. Ther.* 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as Tlymphocytes, Blymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible

by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication  
5 WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the  
10 appropriate inducer of transcription.

#### ***Demonstration of Therapeutic or Prophylactic Activity***

The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then in vivo for the desired therapeutic or prophylactic activity, prior to use in  
15 humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance  
20 with the invention, in vitro assays which can be used to determine whether administration of a specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

#### ***Therapeutic/Prophylactic Administration and Composition***

The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably an antibody of the invention. In a preferred aspect, the compound is substantially purified (e.g., substantially free from substances that limit its  
30 effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

5 Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal,  
10 intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In  
15 addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation  
20 with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by  
25 means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

In another embodiment, the compound or composition can be delivered in a vesicle,  
30 in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler

(eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*)

In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*;  
5 Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger  
10 and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J.Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, *supra*,  
15 vol. 2, pp. 115-138 (1984)).

Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered in vivo to promote expression of its  
20 encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is  
25 known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically  
30 acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more

particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the

composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

***Diagnosis and Imaging***

Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

The invention provides a diagnostic assay for diagnosing a disorder, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine ( $^{125}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{112}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.



One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of <sup>99m</sup>Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

Presence of the labeled molecule can be detected in the patient using methods known in the art for in vivo scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention  
5 include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent  
10 compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance  
15 imaging (MRI).

### *Kits*

The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a  
20 substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be  
25 conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous  
30 polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically immunoreactive with at least

one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically

through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

### **Fusion Proteins**

Any colon and/or colon cancer related polypeptide of the invention can be used to generate fusion proteins. For example, a colon and/or colon cancer related polypeptide, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the colon and/or colon cancer related polypeptide can be used to indirectly detect the second protein by binding to the colon and/or colon cancer related polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, the colon and/or colon cancer related polypeptides can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to colon and/or colon cancer related polypeptides include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

Moreover, fusion proteins may also be engineered to improve characteristics of the colon and/or colon cancer related polypeptide. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the colon and/or colon cancer related polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the colon and/or colon cancer related polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the colon and/or colon cancer related protein. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

As one of skill in the art will appreciate, polypeptides of the present invention and the epitope-bearing fragments thereof described above, can be combined with heterologous polypeptide sequences. For example, the polypeptides of the present invention may be fused with heterologous polypeptide sequences, for example, the polypeptides of the present

invention may be fused with parts of the constant domain of immunoglobulins (IgA, IgE, IgG, IgM) or portions thereof (CH1, CH2, CH3, and any combination thereof, including both entire domains and portions thereof), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., *Nature* 331:84-86 (1988).) Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., *J. Biochem.* 270:3958-3964 (1995).)

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D. Bennett et al., *J. Molecular Recognition* 8:52-58 (1995); K. Johanson et al., *J. Biol. Chem.* 270:9459-9471 (1995).)

Moreover, the colon and/or colon cancer related polypeptides can be fused to marker sequences, such as a peptide which facilitates purification of any colon and/or colon cancer related polypeptide. In preferred embodiments, the marker amino acid sequence is a hexahistidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., *Cell* 37:767 (1984).)

Thus, any of these above fusions can be engineered using the colon and/or colon cancer related polynucleotides or the polypeptides.

**Vectors, Host Cells, and Protein Production**

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques.

- 5 The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The colon and/or colon cancer related polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is  
10 introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40  
15 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon  
20 (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in E. coli and other bacteria. Representative examples of appropriate hosts include,  
25 but are not limited to, bacterial cells, such as E. coli, Streptomyces and Salmonella typhimurium cells; fungal cells, such as yeast cells (e.g., Saccharomyces cerevisiae or Pichia pastoris (ATCC Accession No. 201178)); insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in  
30 the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a,

pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia.

- 5 Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlsbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

- 10 Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

- 15 A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid  
20 chromatography ("HPLC") is employed for purification.

- Polypeptides of the present invention can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast,  
25 higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded  
30 by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal

process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

In one embodiment, the yeast *Pichia pastoris* is used to express any colon and/or colon cancer related protein of the invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolism pathway is the oxidation of methanol to formaldehyde using O<sub>2</sub>. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O<sub>2</sub>. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. See, Ellis, S.B., *et al.*, *Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J., *et al.*, *Yeast* 5:167-77 (1989); Tschopp, J.F., *et al.*, *Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a colon and/or colon cancer related polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

In one example, the plasmid vector pPIC9K is used to express DNA encoding a colon and/or colon cancer related polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a colon and/or colon cancer related protein of the invention by virtue of the strong *AOX1* promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.



In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a colon and/or colon cancer related polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and  
5 growing the yeast culture in the absence of methanol.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic  
10 material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No.  
15 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, *Proteins: Structures and Molecular Principles*, W.H. Freeman & Co., N.Y., and Hunkapiller et al., *Nature*, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or  
25 chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid,  $\alpha$ -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline,  
30 hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, b-alanine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids,

and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

The invention encompasses polypeptides of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH<sub>4</sub>; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the

ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al.*, *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev *et al.*, *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti *et al.*, *Bioconjug. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), see also Malik *et al.*, *Exp. Hematol.* 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to a proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or

cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado *et al.*, *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304 (1992); Francis *et al.*, *Intern. J. of Hematol.* 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ( $\text{ClSO}_2\text{CH}_2\text{CF}_3$ ). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoroethane sulphonyl group.

Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is

incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out

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The number of polyethylene glycol moieties attached to each protein of the invention (*i.e.*, the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado *et al.*, *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304 (1992).

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The polypeptides of the invention may be in monomers or multimers (*i.e.*, dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to monomers and multimers of the polypeptides of the invention, their preparation, and compositions (preferably, Therapeutics) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

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Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer, refers to a multimer containing only polypeptides corresponding to the amino acid sequence of SEQ ID NO:Y or encoded by the cDNA contained in the deposited clone (including fragments, variants, splice variants, and fusion proteins, corresponding to these as described herein). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid

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sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (e.g., containing polypeptides having identical or different amino acid sequences) or a homotrimer (e.g., containing polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

As used herein, the term heteromer refers to a multimer containing one or more heterologous polypeptides (i.e., polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:Y, or contained in the polypeptide encoded by the clone). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the

covalent associations are between the heterologous sequence contained in a Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention containing Flag® polypeptide sequence. In a further embodiment, associations proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the C-terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide components desired to be contained in the multimer of the invention (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or



otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hydrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

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### **Uses of the Polynucleotides**

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

10 The colon and/or colon cancer related polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each polynucleotide of the present invention can be used as a chromosome marker.

15 Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene  
20 corresponding to the SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that  
25 can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome specific-cDNA libraries, and computer mapping techniques (See, e.g., Shuler, Trends Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety).

Precise chromosomal location of the polynucleotides can also be achieved using  
30 fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-

4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes). Preferred polynucleotides correspond to the noncoding regions of the cDNAs because the coding sequences are more likely conserved within gene families, thus increasing the chance of cross hybridization during chromosomal mapping.

Thus, the present invention also provides a method for chromosomal localization which involves (a) preparing PCR primers from colon and/or colon cancer related polynucleotide sequences in Table 1 and (b) screening somatic cell hybrids containing individual chromosomes.

The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g., Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000); and/or Ott, J. Hered. 90:68-70 (1999) each of which is hereby incorporated by reference in its entirety.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) .) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the colon and/or colon cancer related polynucleotide and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in

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some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide  
5 can be used for further linkage analysis.

Thus, the invention provides a method of detecting increased or decreased expression levels of the colon and/or colon cancer related polynucleotides in affected individuals as compared to unaffected individuals using polynucleotides of the present invention and techniques known in the art, including but not limited to the method described in Example  
10 11. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

Thus, the invention also provides a diagnostic method useful during diagnosis of a tissue related disorder, including cancers, involving measuring the expression level of colon and/or colon cancer related polynucleotides in colon or colon cancer tissues or other cells or  
15 body fluid from an individual and comparing the measured gene expression level with a standard colon and/or colon cancer related polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a colon related disorder, including colon cancer, or a specific tissue related disorder.

In still another embodiment, the invention includes a kit for analyzing samples for the  
20 presence of proliferative and/or cancerous polynucleotides derived from a test subject. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a colon and/or colon cancer related polynucleotide and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes defining an internal region of the colon and/or colon cancer related  
25 polynucleotide, where each probe has one strand containing a 31'-mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

Where a diagnosis of a specific tissue related disorder, including, for example, diagnosis of a tumor, has already been made according to conventional methods, the present  
30 invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed colon and/or colon cancer related polynucleotide expression will experience a

worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

By "measuring the expression level of colon and/or colon cancer related polynucleotides" is intended qualitatively or quantitatively measuring or estimating the level of the colon and/or colon cancer related polypeptide or the level of the mRNA encoding the colon and/or colon cancer related polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the colon and/or colon cancer related polypeptide level or mRNA level in a second biological sample). Preferably, the colon and/or colon cancer related polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard colon and/or colon cancer related polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the specific tissue related disorder or being determined by averaging levels from a population of individuals not having a specific tissue related disorder. As will be appreciated in the art, once a standard colon and/or colon cancer related polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

By "biological sample" is intended any biological sample obtained from an individual, body fluid, cell line, tissue culture, or other source which contains colon and/or colon cancer related polypeptide or mRNA. As indicated, biological samples include body fluids (such as sera, plasma, urine, bile, vaginal pool, semen, lymph, synovial fluid and spinal fluid) which contain the colon and/or colon cancer related polypeptide, and tissue sources found to express the colon and/or colon cancer related polypeptide including colon and/or colon cancer. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

The method(s) provided above may preferably be applied in a diagnostic method and/or kits in which colon and/or colon cancer related polynucleotides and/or polypeptides are attached to a solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in US Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with colon and/or colon cancer related polynucleotides attached may be used to identify polymorphisms between the colon and/or colon cancer related polynucleotide sequences, with polynucleotides isolated from a test subject. The knowledge

of such polymorphisms (i.e. their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, such as for example, in reproductive disorders, neural disorders, immune system disorders, muscular disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. Such a method is described in US Patents 5,858,659 and 5,856,104. The US Patents referenced supra are hereby incorporated by reference in their entirety herein.

The present invention encompasses colon and/or colon cancer related polynucleotides that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the preferred form if the colon and/or colon cancer related polynucleotides are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by P. E. Nielsen, M. Egholm, R. H. Berg and O. Buchardt, Science 254, 1497 (1991); and M. Egholm, O. Buchardt, L. Christensen, C. Behrens, S. M. Freier, D. A. Driver, R. H. Berg, S. K. Kim, B. Norden, and P. E. Nielsen, Nature 365, 666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point ( $T_{sub.m}$ ) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

The present invention have uses which include, but are not limited to, detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias

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including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

Pathological cell proliferative disorders are often associated with inappropriate activation of proto-oncogenes. (Germann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in Neoplastic Diseases of the Blood, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Germann et al., supra) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Germann et al., supra) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Germann et al., supra)

For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO 91/15580) However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., Proc. Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness would not be limited to treatment of proliferative disorders of hematopoietic cells and tissues, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes.

In addition to the foregoing, a colon and/or colon cancer related polynucleotide can be used to control gene expression through triple helix formation or through antisense DNA or

RNA. Antisense techniques are discussed, for example, in Okano, J. *Neurochem.* 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., *Nucleic Acids Research* 6: 3073 (1979); Cooney et al., *Science* 241: 456 (1988); and Dervan et al.,  
5 *Science* 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., *Nucl. Acids Res.* 6:3073 (1979); Cooney et al., *Science* 241:456 (1988); and Dervan et al., *Science* 251:1360 (1991) ) or to the  
10 mRNA itself (antisense - Okano, J. *Neurochem.* 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. The oligonucleotide described above can also be delivered to cells such that the antisense RNA or  
15 DNA may be expressed in vivo to inhibit production of colon and/or colon cancer related antigens. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease, and in particular, for the treatment of proliferative diseases and/or conditions.

Polynucleotides of the present invention are also useful in gene therapy. One goal of  
20 gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

25 The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not  
30 suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to tissues, including but not limited to those shown in Table 3 prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

The polynucleotides of the present invention are also useful as hybridization probes for differential identification of the tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In addition, for a number of disorders of the above tissues or cells, significantly higher or lower



levels of gene expression of the polynucleotides/polypeptides of the present invention may be detected in certain tissues (e.g., tissues expressing polypeptides and/or polynucleotides of the present invention and/or cancerous and/or wounded tissues) or bodily fluids (e.g., vaginal pool, lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Thus, the invention provides a diagnostic method of a disorder, which involves: (a) assaying gene expression level in cells or body fluid of an individual; (b) comparing the gene expression level with a standard gene expression level, whereby an increase or decrease in the assayed gene expression level compared to the standard expression level is indicative of disorder.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

### **Uses of the Polypeptides**

Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

Polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J. Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

Antibodies can be used to assay levels of polypeptides encoded by polynucleotides of the invention in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay

labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine ( $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{115\text{m}}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{112}\text{In}$ ,  $^{111}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ),  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ ,  $^{97}\text{Ru}$ ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying colon and/or colon cancer related polypeptide levels in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example,  $^{131}\text{I}$ ,  $^{112}\text{In}$ ,  $^{99\text{m}}\text{Tc}$ , ( $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{115\text{m}}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{112}\text{In}$ ,  $^{111}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ,  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ ,  $^{97}\text{Ru}$ ), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for a digestive system disorder, including but not limited to disorders or diseases of the colon such as colon cancer.

It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of  $^{99\text{m}}\text{Tc}$ . The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which express the polypeptide encoded by a polynucleotide of the invention. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and

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Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (e.g., polypeptides encoded by colon and/or colon cancer related polynucleotides of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example,  $^{213}\text{Bi}$ , or other radioisotopes such as, for example,  $^{103}\text{Pd}$ ,  $^{133}\text{Xe}$ ,  $^{131}\text{I}$ ,  $^{68}\text{Ge}$ ,  $^{57}\text{Co}$ ,  $^{65}\text{Zn}$ ,  $^{85}\text{Sr}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{90}\text{Y}$ ,  $^{153}\text{Sm}$ ,  $^{153}\text{Gd}$ ,  $^{169}\text{Yb}$ ,  $^{51}\text{Cr}$ ,  $^{54}\text{Mn}$ ,  $^{75}\text{Se}$ ,  $^{113}\text{Sn}$ ,  $^{90}\text{Yttrium}$ ,  $^{117}\text{Tin}$ ,  $^{186}\text{Rhenium}$ ,  $^{166}\text{Holmium}$ , and  $^{188}\text{Rhenium}$ ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

Techniques known in the art may be applied to label polypeptides of the invention (including antibodies). Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239;

5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a colon and/or colon cancer related polypeptide of the present invention in cells or body fluid of an individual, or more preferably, assaying the expression level of a colon and/or colon cancer related polypeptide of the present invention in colon and/or colon cancer tissues or associated bodily fluid of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Moreover, colon and/or colon cancer related polypeptides of the present invention can be used to treat or prevent diseases or conditions such as, for example, gastrointestinal disorders, reproductive disorders, neural disorders, immune system disorders, muscular disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor suppressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease (as described supra, and elsewhere herein). For example, administration

of an antibody directed to a polypeptide of the present invention can bind, and/or neutralize the polypeptide, and/or reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

5 At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present  
10 invention can be used to test the following biological activities.

### **Gene Therapy Methods**

Another aspect of the present invention is to gene therapy methods for treating disorders, diseases and conditions. The gene therapy methods relate to the introduction of  
15 nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of the polypeptide of the present invention. This method requires a polynucleotide which codes for a polypeptide operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which  
20 is herein incorporated by reference.

Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide ex vivo, with the engineered cells then being provided to a patient to be treated with the polypeptide. Such methods are well-known in the art. For example, see Belldgrun, A., et al., J. Natl. Cancer  
25 Inst. 85: 207-216 (1993); Ferrantini, M. et al., Cancer Research 53: 1107-1112 (1993); Ferrantini, M. et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura, H., et al., Cancer Research 50: 5102-5106 (1990); Santodonato, L., et al., Human Gene Therapy 7:1-10 (1996); Santodonato, L., et al., Gene Therapy 4:1246-1255 (1997); and Zhang, J.-F. et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein  
30 incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

In one embodiment, the polynucleotide is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

Any strong promoter known to those skilled in the art can be used for driving the expression of polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoA1 promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polypeptide of the present invention.

Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. In vivo muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

In certain embodiments, the polynucleotide constructs are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA (1989) 86:6077-6081, which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem. (1990) 265:10189-10192, which is herein incorporated by reference), in functional form.

Cationic liposomes are readily available. For example, N[1-2,3-dioleoyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphosphatidyl ethanolamine (DOPE), among others. These materials can also be mixed



with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., *Methods of Immunology* (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include  $\text{Ca}^{2+}$ -EDTA chelation (Papahadjopoulos et al., *Biochim. Biophys. Acta* (1975) 394:483; Wilson et al., *Cell* (1979) 17:77); ether injection (Deamer, D. and Bangham, A., *Biochim. Biophys. Acta* (1976) 443:629; Ostro et al., *Biochem. Biophys. Res. Commun.* (1977) 76:836; Fraley et al.,

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Proc. Natl. Acad. Sci. USA (1979) 76:3348); detergent dialysis (Enoch, H. and Strittmatter, P., Proc. Natl. Acad. Sci. USA (1979) 76:145); and reverse-phase evaporation (REV) (Fraleigh et al., J. Biol. Chem. (1980) 255:10431; Szoka, F. and Papahadjopoulos, D., Proc. Natl. Acad. Sci. USA (1978) 75:145; Schaefer-Ridder et al., Science (1982) 215:166), which are  
5 herein incorporated by reference.

Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ratio will be from about 5:1 to about 1:5. More preferably, the ratio will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the  
10 injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no.  
15 WO 94/9469 (which are herein incorporated by reference) provide methods for delivering DNA-cationic lipid complexes to mammals.

In certain embodiments, cells are engineered, ex vivo or in vivo, using a retroviral particle containing RNA which comprises a SEQ ID NO:X. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine  
20 Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are  
25 not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and CaPO<sub>4</sub> precipitation. In one  
30 alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

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The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding SEQ ID NO:Y. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either in vitro or in vivo. The transduced eukaryotic cells will express SEQ ID NO:Y.

5 In certain other embodiments, cells are engineered, ex vivo or in vivo, with polynucleotide of the present invention contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses the polypeptide of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the  
10 host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz, A. R. et al. (1974) Am. Rev. Respir. Dis.109:233-238). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld, M.  
15 A. et al. (1991) Science 252:431-434; Rosenfeld et al., (1992) Cell 68:143-155). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green, M. et al. (1979) Proc. Natl. Acad. Sci. USA 76:6606).

Suitable adenoviral vectors useful in the present invention are described, for example,  
20 in Kozarsky and Wilson, Curr. Opin. Genet. Devel. 3:499-503 (1993); Rosenfeld et al., Cell 68:143-155 (1992); Engelhardt et al., Human Genet. Ther. 4:759-769 (1993); Yang et al., Nature Genet. 7:362-369 (1994); Wilson et al., Nature 365:691-692 (1993); and U.S. Patent No. 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region  
25 of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

Preferably, the adenoviruses used in the present invention are replication deficient.  
30 Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in

most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

In certain other embodiments, the cells are engineered, ex vivo or in vivo, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require  
5 helper viruses to produce infectious particles (Muzyczka, N., Curr. Topics in Microbiol. Immunol. 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos.  
10 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual,  
15 Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral  
20 particles which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either ex vivo or in vivo. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express the polypeptide of the present invention.

Another method of gene therapy involves operably associating heterologous control  
25 regions and endogenous polynucleotide sequences (e.g. encoding the polypeptide of the present invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438  
30 (1989). This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

The polynucleotides encoding the polypeptide of the present invention may be administered along with other polynucleotides encoding an angiogenic protein. Examples of angiogenic proteins include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

Preferably, the polynucleotide encoding the polypeptide of the present invention contains a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be  
5 homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection,  
10 systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppositorial solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct  
15 injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is  
20 administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery  
25 and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise  
30 liposomes comprising ligands for targeting the vehicle to a particular site.

Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using

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methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA 189:11277-11281, 1992, which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly preferred

## **Biological Activities**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, can be used in assays to test for one or more biological activities. If these polynucleotides or polypeptides, or agonists or antagonists of the present invention, do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides, and agonists or antagonists could be used to treat the associated disease.

The colon and/or colon cancer related polynucleotides and/or polypeptides of the invention are expressed at significantly enhanced levels in human colon and colon cancer tissues.

Thus, colon and/or colon cancer related polynucleotides and/or polypeptides of the invention may be useful as a therapeutic molecule. It would be useful for diagnosis, detection, treatment and/or prevention of disorders of the colon, including inflammatory

disorders such as, congenital abnormalities, such as atresia and stenosis, Meckel diverticulum, congenital aganglionic megacolon-Hirschsprung disease; enterocolitis, such as diarrhea and dysentery, infectious enterocolitis, including viral gastroenteritis, bacterial enterocolitis, necrotizing enterocolitis, antibiotic-associated colitis (pseudomembranous colitis), and collagenous and lymphocytic colitis, miscellaneous intestinal inflammatory disorders, including parasites and protozoa, amoebic colitis, acquired immunodeficiency syndrome, transplantation, drug-induced intestinal injury, radiation enterocolitis, neutropenic colitis, diverticular colon disease (DCD), inflammatory colonic disease, idiopathic inflammatory bowel disease, such as Crohn's disease (CD), non-inflammatory bowel disease (non-IBD) colonic inflammation; ulcerative disorders such as, ulcerative colitis (UC); eosinophilic colitis; noncancerous tumors, such as, polyps in the colon, adenomas, leiomyomas, lipomas, and angiomas.

Particularly, the colon and/or colon cancer polynucleotides and/or polypeptides of the invention may be a useful therapeutic for tumors, especially of the intestine, such as, carcinoid tumors, lymphomas, non-neoplastic polyps, adenomas, familial syndromes, colorectal carcinogenesis, colorectal carcinoma, cancer of the colon, cancer of the rectum and carcinoid tumors, as well as cancers in other tissues where expression has been indicated. Treatment, diagnosis, detection, and/or prevention of colon disorders could be carried out using a soluble form of a colon and/or colon cancer polypeptides, the colon and/or colon cancer polypeptides ligand, gene therapy, or ex vivo applications. Moreover, inhibitors of colon and/or colon cancer polynucleotides and/or polypeptides, either blocking antibodies or mutant forms, could modulate the expression of colon and/or colon cancer polynucleotides and/or polypeptides. These inhibitors may be useful to treat, diagnose, detect, and/or prevent diseases associated with the misregulation of colon and/or colon cancer polynucleotides and/or polypeptides.

In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells (e.g., colon or colon cancer cells) by administering polypeptides of the invention (e.g., colon and/or colon cancer polypeptides or anti-colon cancer antigen antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell (e.g., a colon cancer cell). In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double



stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., colon or colon cancer polypeptides or anti-colon cancer antigen antibodies) in association with toxins or cytotoxic prodrugs.

By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, cytotoxins (cytotoxic agents), or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example,  $^{213}\text{Bi}$ , or other radioisotopes such as, for example,  $^{103}\text{Pd}$ ,  $^{133}\text{Xe}$ ,  $^{131}\text{I}$ ,  $^{68}\text{Ge}$ ,  $^{57}\text{Co}$ ,  $^{65}\text{Zn}$ ,  $^{85}\text{Sr}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{90}\text{Y}$ ,  $^{153}\text{Sm}$ ,  $^{153}\text{Gd}$ ,  $^{169}\text{Yb}$ ,  $^{51}\text{Cr}$ ,  $^{54}\text{Mn}$ ,  $^{75}\text{Se}$ ,  $^{113}\text{Sn}$ ,  $^{90}\text{Yttrium}$ ,  $^{117}\text{Tin}$ ,  $^{186}\text{Rhenium}$ ,  $^{166}\text{Holmium}$ , and  $^{188}\text{Rhenium}$ ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

Techniques known in the art may be applied to label antibodies of the invention. Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety). A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g.,

methotrexate, 6-mercaptopurine, 6- thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin),  
5 anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that  
10 may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

It will be appreciated that conditions caused by a decrease in the standard or normal  
15 level of colon and/or colon cancer polynucleotide and/or polypeptide activity in an individual, particularly disorders of the colon, can be treated by administration of colon or colon cancer polypeptide (e.g., in the form of soluble extracellular domain or cells expressing the complete protein) or agonist. Thus, the invention also provides a method of treatment of an individual in need of an increased level of PSGR activity comprising administering to  
20 such an individual a pharmaceutical composition comprising an amount of an isolated colon or colon cancer polypeptide of the invention, or agonist thereof (e.g, an agonistic anti-colon cancer antigen antibody), effective to increase the colon and/or colon cancer polypeptide activity level in such an individual.

It will also be appreciated that conditions caused by a increase in the standard or normal level  
25 of colon and/or colon cancer polynucleotides and/or polypeptides activity in an individual, particularly disorders of the colon, can be treated by administration of colon or colon cancer related polypeptides (e.g., in the form of soluble extracellular domain or cells expressing the complete protein) or antagonist (e.g., an antagonistic anti-colon cancer antigen antibody). Thus, the invention also provides a method of treatment of an individual in need of an  
30 decreased level of colon and/or colon cancer polynucleotides and/or polypeptides activity comprising administering to such an individual a pharmaceutical composition comprising an amount of an isolated colon polypeptide of the invention, or antagonist thereof, effective to

decrease the colon and/or colon cancer polynucleotides and/or polypeptides activity level in such an individual.

## 5 Immune Activity

A polypeptide or polynucleotide, or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing deficiencies, diseases, or disorders and/or conditions of the immune system, by, for example, activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells  
10 develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, polynucleotides or polypeptides, or  
15 agonists or antagonists of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may be useful in treating, preventing, detecting and/or diagnosing diseases, deficiencies or disorders and/or conditions of hematopoietic cells. Polynucleotides or polypeptides, or  
20 agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia,  
25 common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

Moreover, polynucleotides or polypeptides, or agonists or antagonists of the present  
30 invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, polynucleotides or polypeptides, or agonists or antagonists of the

present invention could be used to treat blood coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, polynucleotides or polypeptides, or agonists or antagonists of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be useful in treating, preventing, detecting and/or diagnosing autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of polynucleotides or polypeptides, or agonists or antagonists of the present invention that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Autoimmune diseases or disorders that may be treated, prevented, and/or diagnosed by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, one or more of the following: autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmunocytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (e.g, IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis Ophthalmia, Polyendocrinopathies, Purpura (e.g., Henloch-Schoenlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, Autism, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye, autoimmune thyroiditis, hypothyroidism (i.e., Hashimoto's thyroiditis, systemic lupus erythematosus, Goodpasture's syndrome, Pemphigus, Receptor autoimmunities such as, for example, (a) Graves' Disease, (b) Myasthenia Gravis, and (c) insulin resistance, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, rheumatoid arthritis, scleroderma with anti-collagen antibodies, mixed connective tissue disease, polymyositis/dermatomyositis, pernicious anemia, idiopathic Addison's disease, infertility, glomerulonephritis such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid, Sjogren's syndrome, diabetes mellitus, and adrenergic drug resistance (including adrenergic drug resistance with

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asthma or cystic fibrosis), chronic active hepatitis, primary biliary cirrhosis, other endocrine gland failure, vitiligo, vasculitis, post-MI, cardiomy syndrome, urticaria, atopic dermatitis, asthma, inflammatory myopathies, and other inflammatory, granulomatous, degenerative, and atrophic disorders.

5 Additional autoimmune disorders (that are probable) that may be treated, prevented, and/or diagnosed with the compositions of the invention include, but are not limited to, rheumatoid arthritis (often characterized, e.g., by immune complexes in joints), scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to  
10 extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized,  
15 e.g., by glomerular basement membrane antibodies or immune complexes), bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjogren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug  
20 resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies).

Additional autoimmune disorders (that are possible) that may be treated, prevented, and/or diagnosed with the compositions of the invention include, but are not limited to, chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary  
25 biliary cirrhosis (often characterized, e.g., by mitochondrial antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiomy syndrome (often characterized, e.g., by  
30 myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma

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(often characterized, e.g., by IgG and IgM antibodies to IgE), and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, and/or  
5 diagnosed using for example, antagonists or agonists, polypeptides or polynucleotides, or antibodies of the present invention.

In a preferred embodiment polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among B cell and/or T cell immunodeficient individuals.

10 B cell immunodeficiencies that may be ameliorated or treated by administering the polypeptides or polynucleotides of the invention, and/or agonists thereof, include, but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia,  
15 acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable immunodeficiency (CVI) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked  
20 immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe  
25 congenital leukopenia, thymic aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome-combined immunodeficiency with Igs, purine nucleoside phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

30 T cell deficiencies that may be ameliorated or treated by administering the polypeptides or polynucleotides of the invention, and/or agonists thereof include, but are not limited to, for example, DiGeorge anomaly, thymic hypoplasia, third and fourth pharyngeal

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pouch syndrome, 22q11.2 deletion, chronic mucocutaneous candidiasis, natural killer cell deficiency (NK), idiopathic CD4+ T-lymphocytopenia, immunodeficiency with predominant T cell defect (unspecified), and unspecified immunodeficiency of cell mediated immunity. In specific embodiments, DiGeorge anomaly or conditions associated with DiGeorge anomaly  
5 are ameliorated or treated by, for example, administering the polypeptides or polynucleotides of the invention, or antagonists or agonists thereof.

Other immunodeficiencies that may be ameliorated or treated by administering polypeptides or polynucleotides of the invention, and/or agonists thereof, include, but are not limited to, severe combined immunodeficiency (SCID; e.g., X-linked SCID, autosomal  
10 SCID, and adenosine deaminase deficiency), ataxia-telangiectasia, Wiskott-Aldrich syndrome, short-limber dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome (e.g., purine nucleoside phosphorylase deficiency), MHC Class II deficiency. In specific embodiments, ataxia-telangiectasia or conditions associated with ataxia-telangiectasia are ameliorated or treated by administering the polypeptides or polynucleotides  
15 of the invention, and/or agonists thereof.

In a specific preferred embodiment, rheumatoid arthritis is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In another specific preferred embodiment, systemic lupus erythematosus is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies,  
20 and/or agonists or antagonists of the present invention. In another specific preferred embodiment, idiopathic thrombocytopenia purpura is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In another specific preferred embodiment IgA nephropathy is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or  
25 antagonists of the present invention. In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, and/or diagnosed using antibodies against the protein of the invention.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated, prevented, and/or diagnosed  
30 using polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof. Moreover, these molecules can be used to treat, prevent, and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

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Moreover, inflammatory conditions may also be treated, diagnosed, and/or prevented with polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. Such inflammatory conditions include, but are not limited to, for example, respiratory disorders (such as, e.g., asthma and allergy); gastrointestinal disorders (such as, e.g., inflammatory bowel disease); cancers (such as, e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (such as, e.g., multiple sclerosis, blood-brain barrier permeability, ischemic brain injury and/or stroke, traumatic brain injury, neurodegenerative disorders (such as, e.g., Parkinson's disease and Alzheimer's disease), AIDS-related dementia, and prion disease); cardiovascular disorders (such as, e.g., atherosclerosis, myocarditis, cardiovascular disease, and cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (such as, e.g., chronic hepatitis (B and C), rheumatoid arthritis, gout, trauma, septic shock, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus (i.e., type 1 diabetes), and allogenic transplant rejection).

In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to treat, diagnose, and/or prevent transplantation rejections, graft-versus-host disease, autoimmune and inflammatory diseases (e.g., immune complex-induced vasculitis, glomerulonephritis, hemolytic anemia, myasthenia gravis, type II collagen-induced arthritis, experimental allergic and hyperacute xenograft rejection, rheumatoid arthritis, and systemic lupus erythematosus (SLE). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also be used to modulate and/or diagnose inflammation. For example, since polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to treat, diagnose,



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or prognose, inflammatory conditions, both chronic and acute conditions, including, but not limited to, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, and resulting from over  
5 production of cytokines (e.g., TNF or IL-1).

Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or  
10 differentiation of B and/or T cells, infectious diseases may be treated, detected, and/or prevented. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents,  
15 etc), without necessarily eliciting an immune response.

Additional preferred embodiments of the invention include, but are not limited to, the use of polypeptides, antibodies, polynucleotides and/or agonists or antagonists in the following applications:

Administration to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-  
20 pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response.

Administration to an animal (including, but not limited to, those listed above, and also  
25 including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741.

30 A vaccine adjuvant that enhances immune responsiveness to specific antigen.

An adjuvant to enhance tumor-specific immune responses.

An adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, Respiratory syncytial virus, Dengue, Rotavirus, Japanese B encephalitis, Influenza A and B, Parainfluenza, Measles, Cytomegalovirus, Rabies, Junin, Chikungunya, Rift Valley fever, Herpes simplex, and yellow fever.

An adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae*, *Mycobacterium leprae*, *Salmonella typhi*, *Salmonella paratyphi*, *Meisseria meningitidis*, *Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, *Borrelia burgdorferi*, and Plasmodium (malaria).

An adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria).

As a stimulator of B cell responsiveness to pathogens.

As an activator of T cells.

As an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

As an agent to induce higher affinity antibodies.

5 As an agent to increase serum immunoglobulin concentrations.

As an agent to accelerate recovery of immunocompromised individuals.

As an agent to boost immunoresponsiveness among aged populations.

As an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect  
10 to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but  
15 prior to full recovery of B cell populations.

As an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, HIV Infection, AIDS,  
20 bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

As an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, recovery from viral infections  
25 (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, recovery from surgery.

As a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists  
30 of the present invention enhance antigen presentation or antagonizes antigen presentation in vitro or in vivo. Moreover, in related embodiments, said enhancement or antagonization of

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antigen presentation may be useful as an anti- tumor treatment or to modulate the immune system.

As an agent to direct an individuals immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

5 As a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly their susceptibility profile would likely change.

10 As a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodeficiency.

As a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect.

As a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence such as observed among SCID patients.

15 As an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

As a means of activating T cells.

As a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leshmania.

20 As pretreatment of bone marrow samples prior to transplant. Such treatment would increase B cell representation and thus accelerate recover.

As a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

25 Additionally, polypeptides or polynucleotides of the invention, and/or agonists thereof, may be used to treat or prevent IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema.

All of the above described applications as they may apply to veterinary medicine.

30 Antagonists of the invention include, for example, binding and/or inhibitory antibodies, antisense nucleic acids, or ribozymes. These would be expected to reverse many of the activities of the ligand described above as well as find clinical or practical application as:

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A means of blocking various aspects of immune responses to foreign agents or self. Examples include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and pathogens.

5 A therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythramatosus and MS.

An inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune responses, and blocking sepsis.

10 An inhibitor of graft versus host disease or transplant rejection.

A therapy for B cell and/or T cell malignancies such as ALL, Hodgkins disease, non-Hodgkins lymphoma, Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, and EBV-transformed diseases.

15 A therapy for chronic hypergammaglobulinemia evident in such diseases as monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonal gammopathies, and plasmacytomas.

A therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

A means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

20 An immunosuppressive agent(s).

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate IgE concentrations in vitro or in vivo.

25 In another embodiment, administration of polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention, may be used to treat or prevent IgE-mediated allergic reactions including, but not limited to, asthma, rhinitis, and eczema.

The agonists and antagonists may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as described herein.

30 The agonists or antagonists may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain auto-immune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and

insulin-dependent diabetes. The antagonists or agonists may also be employed to treat infectious diseases including silicosis, sarcoidosis, idiopathic pulmonary fibrosis by, for example, preventing the recruitment and activation of mononuclear phagocytes. They may also be employed to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration. The antagonists or agonists or may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.

Antibodies against polypeptides of the invention may be employed to treat ARDS.

Agonists and/or antagonists of the invention also have uses in stimulating wound and tissue repair, stimulating angiogenesis, stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, agonists and antagonists of the invention may be used to stimulate the regeneration of mucosal surfaces.

In a specific embodiment, polynucleotides or polypeptides, and/or agonists thereof are used to treat or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, polynucleotides or polypeptides, and/or agonists thereof may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carinii.

In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a subset of this disease.

In a specific embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to treat, diagnose, and/or prevent (1) cancers or neoplasms and (2) autoimmune cell or tissue-related cancers or neoplasms. In a preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or

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antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat, diagnose, and/or prevent acute myelogeneous leukemia. In a further preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat, diagnose, and/or prevent, chronic myelogeneous leukemia, multiple myeloma, non-Hodgkins lymphoma, and/or Hodgkins disease.

In another specific embodiment, polynucleotides or polypeptides, and/or agonists or antagonists of the invention may be used to treat, diagnose, prognose, and/or prevent selective IgA deficiency, myeloperoxidase deficiency, C2 deficiency, ataxia-telangiectasia, DiGeorge anomaly, common variable immunodeficiency (CVI), X-linked agammaglobulinemia, severe combined immunodeficiency (SCID), chronic granulomatous disease (CGD), and Wiskott-Aldrich syndrome.

Examples of autoimmune disorders that can be treated or detected are described above and also include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of

polynucleotides or polypeptides, or agonists or antagonists of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be used to modulate inflammation. For example, polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including chronic prostatitis, granulomatous prostatitis and malacoplakia, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prognosed, prevented, and/or diagnosed using antibodies against the polypeptide of the invention.

As an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

Additionally, polynucleotides, polypeptides, and/or antagonists of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the inhibition of apoptosis that could be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis



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and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome,

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Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Hyperproliferative diseases and/or disorders that could be detected and/or treated by polynucleotides, polypeptides, and/or antagonists of the invention, include, but are not limited to neoplasms located in the: liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenström's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

### **Hyperproliferative Disorders**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, Polynucleotides or polypeptides, or agonists or antagonists of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response.

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Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by Polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenström's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

One preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said polynucleotide represses said expression.

Another embodiment of the present invention provides a method of treating cell-proliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the polynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present

invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e. magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e. to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

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The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating one or more of the described disorders. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

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In particular, the antibodies, fragments and derivatives of the present invention are useful for treating a subject having or developing cell proliferative and/or differentiation disorders as described herein. Such treatment comprises administering a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

5       The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example., which serve to increase the number or activity of effector cells which interact with the antibodies.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing  
10   antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragments thereof. Preferred binding affinities include those with a  
15   dissociation constant or  $K_d$  less than  $5 \times 10^{-6}M$ ,  $10^{-6}M$ ,  $5 \times 10^{-7}M$ ,  $10^{-7}M$ ,  $5 \times 10^{-8}M$ ,  $10^{-8}M$ ,  $5 \times 10^{-9}M$ ,  $10^{-9}M$ ,  $5 \times 10^{-10}M$ ,  $10^{-10}M$ ,  $5 \times 10^{-11}M$ ,  $10^{-11}M$ ,  $5 \times 10^{-12}M$ ,  $10^{-12}M$ ,  $5 \times 10^{-13}M$ ,  $10^{-13}M$ ,  $5 \times 10^{-14}M$ ,  $10^{-14}M$ ,  $5 \times 10^{-15}M$ , and  $10^{-15}M$ .

Moreover, polypeptides of the present invention are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other  
20   polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998), which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the  
25   present invention may also result in inhibition of angiogenesis directly, or indirectly (See Witte L, et al., Cancer Metastasis Rev. 17(2):155-61 (1998), which is hereby incorporated by reference)).

Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis.  
30   Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-

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mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the  
5 activation of other proteins which will activate apoptosis, or through stimulating the expression of said proteins, either alone or in combination with small molecule drugs or adjuvants, such as apoptonin, galectins, thioredoxins, antiinflammatory proteins (See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12 (1998), Int J Tissue  
10 React;20(1):3-15 (1998), which are all hereby incorporated by reference).

Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewhere herein, or indirectly, such as activating the expression of  
15 proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such therapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

In another embodiment, the invention provides a method of delivering compositions  
20 containing the polypeptides of the invention (e.g., compositions containing polypeptides or polypeptide antibodies associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. Polypeptides or polypeptide antibodies of the invention may be associated with with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic,  
25 hydrophilic, ionic and/or covalent interactions.

Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly,  
30 such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

**Cardiovascular Disorders**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat cardiovascular disorders, including peripheral artery disease, such as limb ischemia.

5 Cardiovascular disorders include cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, 10 levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilogly of Fallot, ventricular heart septal defects.

Cardiovascular disorders also include heart disease, such as arrhythmias, carcinoid 15 heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, 20 myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

Arrhythmias include sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, 25 extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, 30 ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.



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Heart valve disease include aortic valve insufficiency, aortic valve stenosis, heart murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

Myocardial diseases include alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

Myocardial ischemias include coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

Cardiovascular diseases also include vascular diseases such as aneurysms, angiodyplasia, angiomas, bacillary angiomas, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, ataxia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

Aneurysms include dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

Arterial occlusive diseases include arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

Cerebrovascular disorders include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis,

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carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subarachnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

Embolisms include air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromboembolisms. Thrombosis include coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

Ischemia includes cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, are especially effective for the treatment of critical limb ischemia and coronary disease.

Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

### **Anti-Angiogenesis Activity**

The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al.*, *Cell* 56:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and

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spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis. See, e.g., reviews by Moses *et al.*, *Biotech.* 9:630-634 (1991); Folkman *et al.*, *N. Engl. J. Med.*, 333:1757-1763 (1995); Auerbach *et al.*, *J. Microvasc. Res.* 29:401-411 (1985); Folkman, *Advances in Cancer Research*, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Ophthalmol.* 94:715-743 (1982); and Folkman *et al.*, *Science* 221:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science* 235:442-447 (1987).

The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of the polynucleotides and/or polypeptides of the invention, as well as agonists or antagonists of the present invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.*, *Medicine*, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)). Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non-small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered

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topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical  
5 administration. Polynucleotides, polypeptides, antagonists and/or agonists may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

Polynucleotides, polypeptides, antagonists and/or agonists may be useful in treating  
10 other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis,  
15 retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque  
20 neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering a polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar  
25 or keloid.

Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of  
30 hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also

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provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

Moreover, Ocular disorders associated with neovascularization which can be treated  
5 with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g.,  
10 reviews by Waltman *et al.*, *Am. J. Ophthalm.* 85:704-710 (1978) and Gartner *et al.*, *Surv. Ophthalm.* 22:291-312 (1978).

Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically  
15 effective amount of a compound (as described above) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may  
20 become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact  
25 lenses.

Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily.  
30 Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within

further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma.

Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

Within particularly preferred embodiments of the invention, proliferative diabetic

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retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

5           Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreal injection and/or via intraocular implants.

10           Additionally, disorders which can be treated with the polynucleotides, polypeptides, agonists and/or antagonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

15           Moreover, disorders and/or states, which can be treated with the the polynucleotides, polypeptides, agonists and/or antagonists include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for  
20           example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uveitis, delayed wound healing, endometriosis, vasculogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations,  
25           ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophilic joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochela minalia quintosa), ulcers  
30           (Helicobacter pylori), Bartonellosis and bacillary angiomatosis.

          In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have

occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

5 Polynucleotides, polypeptides, agonists and/or agonists of the present invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

Polynucleotides, polypeptides, agonists and/or agonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an  
10 area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated  
15 with anti- angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

20 Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or agonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the  
25 tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

30 Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or agonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one



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embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

The polynucleotides, polypeptides, agonists and/or agonists of the present invention may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine

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5 sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP-PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including  
10 for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradasulfate; Eponemycin;  
15 Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316,  
20 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolimidazole; and metalloproteinase inhibitors such as BB94.

### **Diseases at the Cellular Level**

20 Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated or detected by polynucleotides or polypeptides, as well as antagonists or agonists of the present invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma,  
25 lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as  
30 herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, polynucleotides,

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polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated or detected by polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host

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disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

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### **Wound Healing and Epithelial Cell Proliferation**

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omenpal graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as

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agonists or antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to treat gastric and duodenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid

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more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associated with the under expression.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and bronchiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of alveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary dysplasia, in premature infants.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetrachloride and other hepatotoxins known in the art).

In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or

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antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

### **Neural Activity and Neurological Diseases**

5           The polynucleotides, polypeptides and agonists or antagonists of the invention may be used for the diagnosis and/or treatment of diseases, disorders, damage or injury of the brain and/or nervous system. Nervous system disorders that can be treated with the compositions of the invention (e.g., polypeptides, polynucleotides, and/or agonists or antagonists), include, but are not limited to, nervous system injuries, and diseases or disorders which result in either  
10 a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the methods of the invention, include but are not limited to, the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1) ischemic lesions, in which a lack of oxygen in a portion of the nervous  
15 system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia; (2) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of the nervous system is destroyed or injured by malignant tissue which is either a nervous system  
20 associated malignancy or a malignancy derived from non-nervous system tissue; (4) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, or syphilis; (5) degenerative lesions, in which a portion of the nervous system  
25 is destroyed or injured as a result of a degenerative process including but not limited to, degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis (ALS); (6) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including, but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease  
30 (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to, diabetes

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(diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including, but not limited to, multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

In one embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of hypoxia. In a further preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia. According to this embodiment, the compositions of the invention are used to treat or prevent neural cell injury associated with cerebral hypoxia. In one non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention, are used to treat or prevent neural cell injury associated with cerebral ischemia. In another non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with cerebral infarction.

In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a stroke. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a stroke.

In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a heart attack. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a heart attack.

The compositions of the invention which are useful for treating or preventing a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, compositions of the invention which elicit any of the following effects may be useful



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according to the invention: (1) increased survival time of neurons in culture either in the presence or absence of hypoxia or hypoxic conditions; (2) increased sprouting of neurons in culture or *in vivo*; (3) increased production of a neuron-associated molecule in culture or *in vivo*, e.g., choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or

5 (4) decreased symptoms of neuron dysfunction *in vivo*. Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may routinely be measured using a method set forth herein or otherwise known in the art, such as, for example, in Zhang *et al.*, *Proc Natl Acad Sci USA* 97:3637-42 (2000) or in Arakawa *et al.*, *J. Neurosci.*, 10:3507-15 (1990); increased sprouting of neurons may be

10 detected by methods known in the art, such as, for example, the methods set forth in Pestronk *et al.*, *Exp. Neurol.*, 70:65-82 (1980), or Brown *et al.*, *Ann. Rev. Neurosci.*, 4:17-42 (1981); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., using techniques known in the art and depending on the molecule to be measured; and motor neuron dysfunction may be

15 measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

In specific embodiments, motor neuron disorders that may be treated according to the invention include, but are not limited to, disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor

20 neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory

25 Neuropathy (Charcot-Marie-Tooth Disease).

Further, polypeptides or polynucleotides of the invention may play a role in neuronal survival; synapse formation; conductance; neural differentiation, etc. Thus, compositions of the invention (including polynucleotides, polypeptides, and agonists or antagonists) may be used to diagnose and/or treat or prevent diseases or disorders associated with these roles,

30 including, but not limited to, learning and/or cognition disorders. The compositions of the invention may also be useful in the treatment or prevention of neurodegenerative disease states and/or behavioural disorders. Such neurodegenerative disease states and/or behavioral

2013

disorders include, but are not limited to, Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception.

5 In addition, compositions of the invention may also play a role in the treatment, prevention and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

Additionally, polypeptides, polynucleotides and/or agonists or antagonists of the invention, may be useful in protecting neural cells from diseases, damage, disorders, or  
10 injury, associated with cerebrovascular disorders including, but not limited to, carotid artery diseases (e.g., carotid artery thrombosis, carotid stenosis, or Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis (e.g., carotid artery thrombosis, sinus thrombosis, or Wallenberg's Syndrome), cerebral  
15 hemorrhage (e.g., epidural or subdural hematoma, or subarachnoid hemorrhage), cerebral infarction, cerebral ischemia (e.g., transient cerebral ischemia, Subclavian Steal Syndrome, or vertebrobasilar insufficiency), vascular dementia (e.g., multi-infarct), leukomalacia, periventricular, and vascular headache (e.g., cluster headache or migraines).

In accordance with yet a further aspect of the present invention, there is provided a  
20 process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, polynucleotides, polypeptides, agonists and/or antagonists of the invention may be used to treat and/or detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can  
25 be used as a marker or detector of a particular nervous system disease or disorder.

Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase  
30 complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms,

2014

canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache and migraine.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, and Hallervorden-Spatz Syndrome.

2015

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which  
5 includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna,  
10 and cerebral malaria.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include meningitis such as arachnoiditis, aseptic meningitis such as viral meningitis which includes lymphocytic choriomeningitis, Bacterial meningitis which includes Haemophilus Meningitis, Listeria  
15 Meningitis, Meningococcal Meningitis such as Waterhouse-Friderichsen Syndrome, Pneumococcal Meningitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningitis, subdural effusion, meningoencephalitis such as uveningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis  
20 syndrome, prion diseases (such as Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie), and cerebral toxoplasmosis.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include central nervous  
25 system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral scleriosis which includes adrenoleukodystrophy, encephalitis  
30 periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis,

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transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as  
5 epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon- Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucopolipidosis such as fucosidosis, neuronal ceroid-  
10 lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity, encephalocele, meningocele,  
15 meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hereditary motor and sensory neuropathies which include Charcot-Marie Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary  
20 Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include  
25 agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation,  
30 hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle

2017

spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, 5 quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and 10 vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex 15 Paramyoclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia, amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes 20 Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia, Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic 25 Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, and Diabetic neuropathies such as diabetic foot.

Additional neurologic diseases which can be treated or detected with polynucleotides, 30 polypeptides, agonists, and/or antagonists of the present invention include nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as

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causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

## 10 **Infectious Disease**

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E,

2019

Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat AIDS.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, include, but not limited to, the following Gram-Negative and Gram-positive bacteria and bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Cryptococcus neoformans, Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia (e.g., Borrelia burgdorferi, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, E. coli (e.g., Enterotoxigenic E. coli and Enterohemorrhagic E. coli), Enterobacteriaceae (Klebsiella, Salmonella (e.g., Salmonella typhi, and Salmonella paratyphi), Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Mycobacterium leprae, Vibrio cholerae, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Meisseria meningitidis, Pasteurellacea Infections (e.g., Actinobacillus, Heamophilus (e.g., Heamophilus influenza type B), Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, Shigella spp., Staphylococcal, Meningiococcal, Pneumococcal and Streptococcal (e.g., Streptococcus pneumoniae and Group B Streptococcus). These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme



2020

Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis (e.g., meningitis types A and B), Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g.,  
5 cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. Polynucleotides or polypeptides, agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, Polynucleotides, polypeptides, agonists or antagonists of the invention are used to treat: tetanus, Diphtheria, botulism, and/or meningitis type B.

10 Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and  
15 Trichomonas and Sporozoans (e.g., Plasmodium virax, Plasmodium falciparum, Plasmodium malariae and Plasmodium ovale). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis.  
20 polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a  
25 polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

### **Regeneration**

30 Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to

repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

5           Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

10           Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could  
15 be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

            Similarly, nerve and brain tissue could also be regenerated by using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, to proliferate and  
20 differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system  
25 diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotides or polypeptides, as well as agonists or antagonists of the present invention.

### **Chemotaxis**

30           Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or

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endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

### **Binding Activity**

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially

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containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labelled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

Following fixation and incubation, the slides are subjected to auto-radiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express the receptor

molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al.*, *Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al.*, *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. *Biotechniques* 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding polypeptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similar, but not

necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Additionally, this invention provides a method of screening compounds to identify  
5 those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and 3[H] thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of  
10 fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of 3[H] thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of 3[H] thymidine. Both agonist and antagonist compounds may be identified by this procedure.

15 In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the  
20 receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

All of these above assays can be used as diagnostic or prognostic markers. The  
25 molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

30 Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a colon and/or colon cancer polynucleotides and/or polypeptides polypeptide

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of the invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a colon and/or colon cancer polynucleotides and/or polypeptides polypeptide of the invention, (b) assaying a biological activity, and (b) 5 determining if a biological activity of the polypeptide has been altered.

### **Colon Cancer Antigen Binding Peptides and Other Molecules**

The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind the colon cancer antigens of the invention, and the colon cancer 10 antigen binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the colon cancer antigens of the invention. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

This method comprises the steps of:

- 15 a. contacting a colon cancer antigen of the invention with a plurality of molecules; and
- b. identifying a molecule that binds the colon cancer antigen.

The step of contacting the colon cancer antigen of the invention with the plurality of molecules may be effected in a number of ways. For example, one may contemplate 20 immobilizing the colon cancer antigen on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized colon cancer antigen. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized colon cancer antigen of the invention. The molecules having a selective affinity for the colon cancer antigen can then be purified by affinity 25 selection. The nature of the solid support, process for attachment of the colon cancer antigen of the invention to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

Alternatively, one may also separate a plurality of polypeptides into substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can 30 separate the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be

expressed on or about its outer surface (e.g., a recombinant phage). Individual isolates can then be "probed" by a colon cancer antigen, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the colon cancer antigen and the individual clone. Prior to contacting the colon cancer antigen of the invention with each fraction comprising individual polypeptides, the polypeptides could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of transformed host cells of an expression library, which harbor a DNA construct encoding a polypeptide having a selective affinity for protein of the invention. Furthermore, the amino acid sequence of the polypeptide having a selective affinity for a colon cancer antigen of the invention can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypeptide itself, one may use microsequencing techniques. The sequencing technique may include mass spectroscopy.

In certain situations, it may be desirable to wash away any unbound colon cancer antigen, or alternatively, unbound polypeptides, from a mixture of the colon cancer antigen of the invention and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction. Such a wash step may be particularly desirable when the protein of the invention or the plurality of polypeptides is bound to a solid support.

The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide libraries which can be screened for molecules that specifically bind to a protein of the invention. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and in vitro translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., 1991, Science 251:767-773; Houghten et al., 1991, Nature 354:84-86; Lam et al., 1991, Nature 354:82-84; Medynski, 1994, Bio/Technology 12:709-710; Gallop et al., 1994, J. Medicinal Chemistry 37(9):1233-1251; Ohlmeyer et al., 1993, Proc. Natl. Acad. Sci. USA 90:10922-10926; Erb et al., 1994, Proc. Natl. Acad. Sci. USA 91:11422-11426; Houghten et al., 1992, Biotechniques 13:412; Jayawickreme et al., 1994, Proc. Natl. Acad. Sci. USA 91:1614-1618; Salmon et al., 1993,



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Proc. Natl. Acad. Sci. USA 90:11708-11712; PCT Publication No. WO 93/20242; and Brenner and Lerner, 1992, Proc. Natl. Acad. Sci. USA 89:5381-5383.

Examples of phage display libraries are described in Scott and Smith, 1990, Science 249:386-390; Devlin et al., 1990, Science, 249:404-406; Christian, R. B., et al., 1992, J. Mol. Biol. 227:711-718); Lenstra, 1992, J. Immunol. Meth. 152:149-157; Kay et al., 1993, Gene 128:59-65; and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

In vitro translation-based libraries include, but are not limited to, those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis et al., 1994, Proc. Natl. Acad. Sci. USA 91:9022-9026.

By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) can be adapted for use. Peptoid libraries (Simon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371) can also be used. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al. (1994, Proc. Natl. Acad. Sci. USA 91:11138-11142).

The variety of non-peptide libraries that are useful in the present invention is great. For example, Ecker and Crooke, 1995, Bio/Technology 13:351-360 list benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

Non-peptide libraries can be classified broadly into two types: decorated monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

Non-peptide oligomer libraries utilize a large number of monomers that are assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one

monomer, giving the libraries added flexibility.

Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, *Adv. Exp. Med. Biol.* 251:215-218; Scott and Smith, 1990, *Science* 249:386-390; Fowlkes et al., 1992, *BioTechniques* 13:422-427; Oldenburg et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:5393-5397; Yu et al., 1994, *Cell* 76:933-945; Staudt et al., 1988, *Science* 241:577-580; Bock et al., 1992, *Nature* 355:564-566; Tuerk et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:6988-6992; Ellington et al., 1992, *Nature* 355:850-852; U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.;  
10 Rebar and Pabo, 1993, *Science* 263:671-673; and CT Publication No. WO 94/18318.

In a specific embodiment, screening to identify a molecule that binds a colon cancer antigen can be carried out by contacting the library members with a colon cancer antigen of the invention immobilized on a solid phase and harvesting those library members that bind to the colon cancer antigen. Examples of such screening methods, termed "panning" techniques  
15 are described by way of example in Parmley and Smith, 1988, *Gene* 73:305-318; Fowlkes et al., 1992, *BioTechniques* 13:422-427; PCT Publication No. WO 94/18318; and in references cited herein.

In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields and Song, 1989, *Nature* 340:245-246; Chien et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:9578-9582) can be used to identify molecules that specifically bind to a colon and/or  
20 colon cancer related protein of the invention.

Where a colon cancer antigen of the invention binding molecule is a polypeptide, the polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is  
25 used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the  
30 same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occur every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine. Clearly, many types of biases can

be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

5 As mentioned above, in the case of a colon and/or colon cancer related protein of the invention binding molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a colon and/or colon cancer related protein of the invention binding polypeptide has in the range of 15-100  
10 amino acids, or 20-50 amino acids.

The selected colon cancer antigen protein of the invention binding polypeptide can be obtained by chemical synthesis or recombinant expression.

### 15 Targeted Delivery

In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a colon cancer antigen of the invention.

As discussed herein, polypeptides or antibodies of the invention may be associated  
20 with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method  
25 for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific destruction  
30 of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

### Drug Screening

Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a polypeptide of the present invention.

Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the present invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

#### **Antisense And Ribozyme (Antagonists)**

In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained in the deposited clone identified in Table 1. In one embodiment, antisense sequence is generated internally, by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, J., Neurochem. 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of

Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, J., *Neurochem.* 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., *Nucleic Acids Research* 6:3073 (1979); Cooney et al., *Science* 241:456 (1988); and Dervan et al., *Science* 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoR1 site on the 5' end and a HindIII site on the 3' end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl<sub>2</sub>, 10mM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoR1/Hind III site of the retroviral vector PMV7 (WO 91/15580).

For example, the 5' coding portion of a polynucleotide that encodes the polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the

art, used for replication and expression in vertebrate cells. Expression of the sequence encoding the polypeptide of the present invention or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, *Nature* 29:304-310 (1981)), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., *Cell* 22:787-797 (1980)), the herpes thymidine promoter (Wagner et al., *Proc. Natl. Acad. Sci. U.S.A.* 78:1441-1445 (1981)), the regulatory sequences of the metallothionein gene (Brinster, et al., *Nature* 296:39-42 (1982)), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of the present invention. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, *Nature* 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding regions of shown in Table 1 could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region

of mRNA of the present invention, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

5       The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors in  
10   vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., 1988, BioTechniques 6:958-  
15   976) or intercalating agents. (See, e.g., Zon, 1988, Pharm. Res. 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

      The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil,  
20   5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine,  
25   7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-  
30   3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.



The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

5 In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

10 In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641). The oligonucleotide is a 2'-O-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

15 Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

20 While antisense nucleotides complementary to the coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred.

Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 25 1990; Sarver et al, Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. 30 The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of

SEQ ID NO:X. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express in vivo. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirable in cases such as restenosis after balloon angioplasty.

The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

The antagonist/agonist may also be employed to treat the diseases described herein. Thus, the invention provides a method of treating disorders or diseases, including but not limited to the disorders or diseases listed throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

### 30 Other Activities

A polypeptide, polynucleotide, agonist, or antagonist of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in

treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

- 5 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

- 10 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may have the ability to stimulate chondrocyte  
15 growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

- 20 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

- 25 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

- 30 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, circadian rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

### **Other Preferred Embodiments**

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier in Table 2.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in a cDNA library shown in Table 9 which was

deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier in Table 2.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Id in Table 1 which DNA molecule is contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a protein identified in Table 1, wherein the method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the

group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit  
5 Numbers shown above for said cDNA library identifier. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a DNA microarray or "chip" of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 100, 150, 200, 250, 300,  
10 500, 1000, 2000, 3000 or 4000 nucleotide sequences, wherein at least one sequence in said DNA microarray or "chip" is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and  
15 contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least  
20 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

25 Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y wherein Y is any  
30 integer as defined in Table 1.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete



amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

5 Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier in Table 2.

10 Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown  
15 above for said cDNA library identifier.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited  
20 with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in  
25 Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid  
30 sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was

deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an

amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the  
5 ATCC Deposit Numbers shown above for said cDNA library identifier.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10  
10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least  
15 two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA  
20 library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence  
25 which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a  
30 cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide  
5 comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers  
10 shown above for said cDNA library identifier.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the  
15 recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a  
20 human protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Protein of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and said position of the First Amino Acid of the Protein of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a protein encoded by a human cDNA clone identified by a  
25 cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Also preferred is a method of treatment of an individual in need of an increased level of a protein activity, which method comprises administering to such an individual a  
30 Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to increase the level of said protein activity in said individual.

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Also preferred is a method of treatment of an individual in need of a decreased level of a protein activity, which method comprises administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding  
5 fragment of the claimed invention effective to decrease the level of said protein activity in said individual.

Also preferred is a method of treatment of an individual in need of a specific delivery of toxic compositions to diseased cells (e.g., including, but not limited to, colon or colon cancer cells or tissues), which method comprises administering to such an individual a  
10 Therapeutic comprising an amount of an isolated polypeptide of the invention, including, but not limited to a binding agent, or antibody of the claimed invention that are associated with toxin or cytotoxic prodrugs.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not  
15 intended as limiting.

### *Examples*

#### *Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample*

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 9 identifies the vectors used to construct the cDNA library from which each clone was isolated.

Table 9.

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HASA	Uni-ZAP XR	LP03
HFCA HFCD HFCE HFCF	Uni-ZAP XR	LP13
HFKF	Uni-ZAP XR	LP13
HE8A HE8B HE8C HE8D HE8E HE8F HE8N HE8O HE8P HE8Q HE8T HE8U	Uni-ZAP XR	LP03
HGBA HGBG HGBH	Uni-ZAP XR	LP13
HGBB	Uni-ZAP XR	LP03
HHFA	pBluescript	NA
HLHA HLHB HLHC HLHD HLHE HLHG	Uni-ZAP XR	LP03
HOOA	pBluescript	NA
HPLB	Uni-ZAP XR	NA
HPMD HPME HPMF	Uni-ZAP XR	LP03
HPRA	Uni-ZAP XR	LP13
HSIA HSIC HSID HSIE	Uni-ZAP XR	LP03
HTEA HTEB HTEC HTED HTEE HTEF HTEG HTEH HTEJ HTEK	Uni-ZAP XR	LP13
HTPA HTPC	Uni-ZAP XR	LP03
HTTB HTTC HTTD HTTE HTTF	Uni-ZAP XR	LP13
HAPA HAPC	Uni-ZAP XR	LP03
HETA HETB HETC HETD HETG HETH HETI HETJ	Uni-ZAP XR	LP03
HHFB HHFC HHFG HHFH HHFI	Uni-ZAP XR	LP13
HHPE HHPG	Uni-ZAP XR	LP03
HCE1 HCE2 HCE3 HCE4 HCEC HCED HCEE HCEF HCEI HCEM HCEN HCEO HCEP	Uni-ZAP XR	LP03
HUVC HUVD	Uni-ZAP XR	LP13
HUKB HUKF	Lamda ZAP II	LP13
HTHC HTHD	Uni-ZAP XR	LP13
HSTA	Uni-ZAP XR	LP13
HTAE	Uni-ZAP XR	LP13
HLEA	Uni-ZAP XR	PA005 Phage
HFEA HFEB	Uni-ZAP XR	LP13
HJPA HJPC	Uni-ZAP XR	LP13
HCNA	Lambda ZAP II	LP01
HTSG	pBS	LP05
HLTA HLTB HLTC HLTD HLTE	Uni-ZAP XR	LP03
HAHS	pBluescript	LP13
HALS	Uni-ZAP XR	LP13
HE6B HE6F HE6G	Uni-ZAP XR	LP04
HF6S	pBluescript	LP13
HPMS	pBluescript	LP03
HTYS	pBluescript	NA
HRDB HRDD HRDE HRDF	Uni-ZAP XR	LP03
HCAB	Uni-ZAP XR	LP13
HL3A	Uni-ZAP XR	PA005 Phage
HRGD	Uni-ZAP XR	LP13
HSSE HSSG HSSJ	Uni-ZAP XR	LP04
HSUA HSUB	Uni-ZAP XR	LP03
HT3A	Uni-ZAP XR	NA

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LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HT4C	Uni-ZAP XR	LP03
HE9F HE9H HE9M HE9N HE9O HE9P HE9Q HE9R HE9S HE9T	Uni-ZAP XR	LP13
HEPA HEPB	Uni-ZAP XR	LP04
HSFA	Uni-ZAP XR	LP13
HATA HATB HATC HATE	Uni-ZAP XR	LP13
HT3B	Uni-ZAP XR	PA005 Phage
HSNA	Uni-ZAP XR	LP04
HPFC	Uni-ZAP XR	LP04
HE2A HE2D HE2E HE2H HE2I HE2O	Uni-ZAP XR	LP13
HE2B HE2C HE2F HE2P	Uni-ZAP XR	LP13
HCBB	Uni-ZAP XR	NA
HFGA	Uni-ZAP XR	LP03
HNEA HNED	Uni-ZAP XR	LP13
HBGB	Uni-ZAP XR	LP03
HKCA	Uni-ZAP XR	PA005 Phage
HKLA	Lambda ZAP II	PA005 Phage
HBNA	Uni-ZAP XR	LP03
HCET	pBluescript	PA005 Phage
HKCS HKCU	pBluescript	LP03
HKCT	pBluescript	PA005 Phage
HLIS	pBluescript	LP13
HLHS HLHT	pBluescript	LP13
HPRT	pBluescript	PA005 Phage
HPTT	Uni-ZAP XR	LP13
HRGS	pBluescript	LP03
HSUS	pBluescript	LP13
HT2S	Uni-ZAP XR	NA
HCNS	pBluescript	PA005 Phage
HCNU	pBluescript	PA005 Phage
HKLR	pBluescript	PA005 Phage
HKLS	pBluescript	PA005 Phage
HKTA	Uni-ZAP XR	PA005 Phage
HHFU	pBluescript	NA
HE8S	Uni-ZAP XR	LP03
HCDC HCDE	Uni-ZAP XR	LP03
HOAA	Uni-ZAP XR	LP13
HTLA HTLD HTLE	Uni-ZAP XR	LP03
HLMD	Uni-ZAP XR	PA005 Phage
HLMI HLMM	Lambda Zap II	LP01

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LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
H6EA H6EB	Uni-ZAP XR	LP03
HCEV HCEY	Uni-ZAP XR	LP03
HCQA HCQB	Lambda Zap II	LP01
HTOA HTOD HTOH HTOJ	Uni-ZAP XR	LP13
HTXC HTXF	Uni-ZAP XR	LP03
HMEC HMEE HMEG HMEI HMEK	Lambda Zap II	LP01
HMEB	Lambda Zap II	LP13
HNFE HNFF HNFG HNFH	Uni-ZAP XR	LP03
HKEA	ZAP express	PA005 Phage
HMGB	Uni-ZAP XR	LP13
HMHB	Uni-ZAP XR	PA005 Phage
HAUA HAUB	Uni-ZAP XR	LP13
HAQB	Uni-ZAP XR	LP13
HCWH	ZAP express	LP02
HCUC	ZAP express	LP02
HSVB HSVC	Uni-ZAP XR	LP03
HPXA	pBluescript	NA
HBJE HBJF HBJJ HBJM	Uni-ZAP XR	LP13
HCRB	Uni-ZAP XR	LP03
HODA HODB HODC HODD	Uni-ZAP XR	LP13
HDSA	Uni-ZAP XR	LP03
HLQA HLQB	Lambda Zap II	LP01
HHGC HHGD	Lambda Zap II	LP01
HCPA	Uni-ZAP XR	LP13
HMWA HMWB HMWD HMWF HMWH HMWI	Uni-ZAP XR	LP03
HERA	Uni-ZAP XR	LP13
HGLA	Uni-ZAP XR	LP13
HWTB HWTC	Uni-ZAP XR	LP13
HLLC	pCMVSPORT1	PA005 DNA
HLIB HLIC	pCMVSPORT1	LP12
HKDB	pCMVSPORT1	NA
HRKA	pBluescript	PA005 Phage
HOSX	pBluescript	PA005 Phage
HEAA	Uni-ZAP XR	LP13
HBCB HBCC	Uni-ZAP XR	LP21
HHBE HHBF HHBH	pCMVSPORT1	LP12
HBBB	pCMVSPORT1	LP12
HLJB HLJD HLJE	pCMVSPORT1	LP12
HSEB	pCMVSPORT1	NA
HNAA	pSPORT1	NA
HBSA	Uni-ZAP XR	LP04
HBBM	pCMVSPORT1	NA
HADM	pBluescript	NA
HMKA HMKC	pSPORT1	LP12
HFVH HFVI HFVJ HFVK	pBluescript	LP03
HKIM	Lambda Zap II	PA005 Phage



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LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HCUD HCUE HCUG	ZAP express	LP02
HKIS	pBluescript	NA
HSDS	pBluescript	LP13
HBAG HBAH	pSport1	NA
HUSG HUSI HUSJ	pSport1	LP10
HUSX HUSY HUSZ	pSport1	LP10
HOFM	pCMVSPORT 2.0	LP07
HNFI	pBluescript	LP03
HBMC HBMD	pBluescript	LP03
HCFB HCFC HCFD	pSport1	LP12
HCFL HCFM HCFN HCFO	pSport1	LP12
HPTW	pBluescript	PA005 Phage
HADC HADF	pSport1	LP10
HOVA HOVC HOVD HOVE	pSport1	LP10
HKML HKMM	pBluescript	LP03
HUSF	pBluescript	NA
HOGA HOGB HOGC HOGD HOGE	pCMVSPORT 2.0	LP12
HTWB HTWC HTWD HTWE HTWF	pSport1	LP10
HBXF	ZAP express	LP02
HEOA	pBluescript	PA005 DNA
HSDX	pBluescript	LP13
HMMA	pSport1	LP12
HLYA HLYB HLYC HLYD HLYE HLYG	pSport1	LP10
HCGL	pCMVSPORT 2.0	LP07
HSDZ	pBluescript	LP13
HEON HEOQ HEOS	pSport1	LP10
HCGB	pSport1	LP10
HADT	pBluescript	NA
HTDA	pSport1	LP12
HSPA HSPB	pSport1	LP10
HSPM	pSport1	LP10
HCHA HCHB HCHC	pSport1	LP10
HCHM HCHO	pSport1	LP10
HDLA	pCMVSPORT 2.0	LP07
HDTA HDTB HDTD HDTE HDTG HDTH HDTI HDTJ HDTK HDTL HDTM	pCMVSPORT 2.0	LP07
HTJM HTJN	pCMVSPORT 2.0	LP12
HCIA	pSport1	LP10
H6BS	Uni-ZAP XR	LP03
HKAA HKAB HKAC HKAD HKAE HKAF HKAH HKAJ HKAK HKAQ	pCMVSPORT 2.0	LP07
HDAA HDAB HDAC	pSport1	LP10
HUFA HUFB HUFC HUFD HUFF	pSport1	LP10
HLDB HLDC HLDD	pCMVSPORT 3.0	LP08

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LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HLDN HLDO	pCMVSPORT 3.0	LP08
HNDA	pCMVSPORT 2.0	LP07
HMTA HMTB	pCMVSPORT 3.0	LP08
HNTA HNTB HNTC HNTD HNTE	pCMVSPORT 3.0	LP08
HNTM	pSPORT1	LP10
HDPA HDPB HDPC HDPF HDPG HDPH HDPI HDPJ HDPK HDPL HDPR HDPS HDPT HDPV HDPW HDPX HDQD HDQE HDQF HDQG HDQH	pCMVSPORT 3.0	LP08
HDPM HDPO HDPP HDPQ HDQP	pCMVSPORT 3.0	LP08
HMTM	PCR11	LP09
HLDX	pSPORT1	LP10
HMUB	pCMVSPORT 3.0	LP08
HULA HULC	pSPORT1	LP10
HFNA	pSPORT1	LP10
HKGA HKGB HKGC HKGD	pSPORT1	LP10
HISA HISB HISC HISD HISE	pSPORT1	LP10
HLSA	pSPORT1	LP10
HHEA HHEB HHEC HHED HHEE HHEF HHEG HHEH HHEI HHEJ	pCMVSPORT 3.0	LP08
HHEM HHEN HHEP HHEQ HHER HHET HHEU HHEV HHEW HHEX HHEY HHEZ	pCMVSPORT 3.0	LP08
HEQA	pCMVSPORT 3.0	LP08
HJMA HJMB	pCMVSPORT 3.0	LP08
HSWB	pCMVSPORT 3.0	LP08
HNTR HNTS HNTT	pSPORT1	NA
HEEA	Uni-ZAP XR	NA
HEGA	Uni-ZAP XR	NA
HSYA HSYB HSYD HSYE	pCMVSPORT 3.0	LP08
HLWA HLWB HLWC	pCMVSPORT 3.0	LP08
HRAA HRAB HRAC HRAE	pCMVSPORT 3.0	LP08
HTXJ HTXK HTXL HTXM HTXO HTXP HTXQ HTXR HTXS	Uni-ZAP XR	LP03
H6ED	Uni-ZAP XR	LP03
HAMF HAMG	pCMVSPORT 3.0	LP12
HAJA HAJB	pCMVSPORT 3.0	LP12
HDFU	pCMVSPORT 2.0	NA
HDHE	pCMVSPORT 2.0	NA
HLQD HLQE HLQF	Lamda ZAP II	LP13

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LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HAPN HAPO HAPQ HAPR	Uni-ZAP XR	LP13
HWBA HWBB HWBC HWBD HWBE HWBF	pCMVSPORT 3.0	LP12
HWAA HWAB HWAC HWAD HWAG HWAJ	pCMVSPORT 3.0	LP12
HYAA HYAB HYAC	pCMVSPORT 3.0	LP12
HWHG HWHH	pCMVSPORT 3.0	LP12
HWHP HWHQ	pCMVSPORT 3.0	LP12
HCWU	ZAP Express	LP13
HSIF HSIG	Uni-ZAP XR	PA005 Phage
HLTG HLTH HLTJ	Uni-ZAP XR	LP13
HARM HARN	pCMVSPORT 3.0	LP12
HBIM HBIN HBIO HBIP	pCMVSPORT 3.0	LP12
HSOB HSOD	Uni-ZAP XR	LP03
HCQC HCQD	Lambda ZAP II	LP01
HCNC HCND	Lambda ZAP II	LP01
HROB HROD	Uni-ZAP XR	LP03
HAHC	Uni-ZAP XR	LP13
HWDA	pCMVSPORT 3.0	LP12
HODE HODF HODG	Uni-ZAP XR	LP03
HTEL HTEP	Uni-ZAP XR	LP03
HBGM HBGN	Uni-ZAP XR	LP03
HTLG HTLH	Uni-ZAP XR	LP03
HHFJ HHFL HHFM	Uni-ZAP XR	LP03
HFKH HFKI HFKM	Uni-ZAP XR	LP03
HTPF HTPG HTPH HTPJ	Uni-ZAP XR	LP03
HUVF HUVG HUVH	Uni-ZAP XR	LP03
HE2J HE2L HE2R HE2T	Uni-ZAP XR	LP04
HS2A	pSport1	LP16
HS2S	pSport1	LP16
HLQG	Lambda Zap II	LP01
HA5A HA5B	pSport1	LP16
HTTI HTTK	Uni-ZAP XR	LP03
HTAH	Uni-ZAP XR	LP03
HDDN	pSport1	LP22
HPCI	Lambda Zap- CMV XR	LP21
HPCR	Lambda Zap- CMV XR	LP22
HPMK HPML	Uni-ZAP XR	LP03
HHFO	Uni-ZAP XR	LP03
HAAA	pSport1	LP22
HOOH	pSport1	LP22
HIDA	pSport1	LP22
HNOA	pSport1	LP22

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LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HMCD	Uni-ZAP XR	LP04
HPCA	Uni ZAP XR	NA
HPHA	Uni-ZAP XR	LP04
HPIA HPIC	Uni-ZAP XR	LP13
HPJA HPJB HPJC HPJE	Uni-ZAP XR	LP13
HFIA HFIB HFIC	pSport1	LP10
HFIH HFII HFIJ	pSport1	LP10
HFIU	pSport1	LP10
HSKX	pBluescript	LP03
HGCO	pSport1	NA
HMVA HMVB HMVC HMVD	pSport1	LP10
HOSE HOSF	Uni-ZAP XR	LP04
HNHN HNHO	Uni ZAP XR	LP04
HTGE HTGF	Uni-ZAP XR	LP04
HFPB HFPC HFPE HFPF HFPH HFPI HFPJ HFPK	Uni-ZAP XR	LP03
HFIX HFIY HFIZ	pSport1	LP10
HOHA HOHB HOHC HOHE	pCMVSPORT 2.0	LP07
HSDJ HSDK	Uni-ZAP XR	LP03
HFOX HFOY	pSport1	LP10
HMAH HMAJ HMAK HMAM	Uni-ZAP XR	LP04
HACB HACC	Uni-ZAP XR	LP04
HFXK	Lambda ZAP II	PA005 Phage
HFAT	Uni ZAP XR	PA005 Phage
HANG	pSport1	NA
HOUH	Uni ZAP XR	NA
HMCF HMCB HMCH HMCI	Uni-ZAP XR	LP13
HWLE HWLF HWLG HWLH HWMA	pSport1	LP14
HCRM HCRN HCRO HCRP HCRQ	pSport1	LP14
HWLI HWLJ HWLK HWLL HWMF	pSport1	LP14
HWLQ HWLR HWLU HWLV HWLW HWLX	pSport1	LP14
HBOD HBOE	pSport1	LP14
HBKD	pSport1	LP14
HWLA HWLC HWLD HWLP	pSport1	LP14
HWLM HWLN HWLO HWMB HWMC	pSport1	LP14
HVAA	pSport1	LP12
HBWC	ZAP express	LP13
HHSF HHSG	Uni ZAP XR	LP04
HSLJ	Uni ZAP XR	NA
HAQN	pSport1	LP14
HASM	pSport1	LP14
HCDM	pSport1	LP14
HFDM	pSport1	LP14
HGAM	pSport1	LP14
HHMM	pSport1	LP14
HAVM	pT-Adv	LP14
HAVT	pT-Adv	LP14
HHAT HHAU	pT-Adv	LP14
HUCN HUCO HUCP HUCQ	pSport1	LP20
HHAO	pCMVSPORT	LP15

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LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
	3.0	
HTFN	pSport1	LP16
HMSM HMSO HMSP	Uni ZAP XR	PA005 Phage
HEPN	pSport1	LP20
HPSN	pSport1	LP20
HNSA	pSport1	LP20
HNSM	pSport1	LP20
HOCN	pSport1	LP20
HOCT	pSport1	LP20
HLXN	pSport1	LP20
HTYN	pSport1	LP20
HZAA	pSport1	LP20
HINA	pSport1	LP16
HRMA	pSport1	LP16
HSKI HSKJ HSKK	pBluescript	LP03
HACA	Uni-ZAP XR	LP13
HFAA HFAC HFAD	Uni-ZAP XR	LP04
HFAM	Uni-ZAP XR	LP04
HMIA HMIB	Uni-ZAP XR	LP04
HILB HILC	pBluescript SK-	PA005 Phage
HPBE	pBluescript SK-	LP13
HIBC HIBE	Other	NA
HPDD	pBluescript SK-	NA
HSAA HSAB HSAC	pBluescript	LP05
HSBA	pBluescript SK-	LP13
HJAA HJAC	pBluescript SK-	LP13
HJBA HJBC	pBluescript SK-	LP13
HAFB	pBS	LP05
HTNA HTNB	pBluescript SK-	LP13
HONA	pBluescript	LP05
HBMA	pBluescript SK-	NA
HARA	pBluescript	LP05
H2CA	pBluescript SK-	NA
H2MA	pBluescript SK-	NA
H2MB H2MC	pBluescript SK-	PA005 Phage
H2CB	pBluescript SK-	PA005 Phage
HCYA	pBluescript SK-	NA
HCYB	pBluescript	PA005

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LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
	SK-	Phage
H2LA H2LB	pBluescript SK-	PA005 Phage

In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

	<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited Plasmid</u>
	Lambda Zap	pBluescript (pBS)
	Uni-Zap XR	pBluescript (pBS)
10	Zap Express	pBK
	lafmid BA	plafmid BA
	pSport1	pSport1
	pCMVSPORT 2.0	pCMVSPORT 2.0
	pCMVSPORT 3.0	pCMVSPORT 3.0
15	pCR <sup>®</sup> 2.1	pCR <sup>®</sup> 2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the fl origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).)



Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from  
5 Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in  
10 Table 2 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 2 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA  
15 clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that library in Table 2 and 9. First, a plasmid is directly isolated by screening the libraries using a polynucleotide probe corresponding to SEQ ID NO:X.

20 Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with <sup>32</sup>P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid  
25 mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using  
30 Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring

Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25  $\mu$ l of reaction mixture with 0.5  $\mu$ g of the above cDNA template. A convenient reaction mixture is 1.5-5 mM  $MgCl_2$ , 0.01% (w/v) gelatin, 20  $\mu$ M each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., *Nucleic Acids Res.* 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of

the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template  
5 for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

### 10 ***Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide***

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

15

### ***Example 3: Tissue specific expression analysis***

The Human Genome Sciences, Inc. (HGS) database is derived from sequencing tissue specific cDNA libraries. Libraries generated from a particular tissue (e.g., those shown in  
20 Table 3 and 5) are selected and the specific tissue expression pattern of EST groups or assembled contigs within these libraries is determined by comparison of the expression patterns of those groups or contigs within the entire database. ESTs which are predicted to have significantly enhances expression in colon or colon cancer tissues were selected.

The original clone from which the specific EST sequence was generated, is obtained  
25 from the catalogued library of clones and the insert amplified by PCR using methods known in the art. The PCR product is denatured then transferred in 96 well format to a nylon membrane (Schleicher and Scheull) generating an array filter of colon and/or colon cancer related clones. Housekeeping genes, maize genes, known tissue specific genes and known membranè localized class I genes are included on the filters as controls. These targets can be  
30 used in signal normalization and to validate assay sensitivity. Additional targets are included to monitor probe length and specificity of hybridization.

Radioactively labeled hybridization probes are generated by first strand cDNA synthesis per the manufacturer's instructions (Life Technologies) from mRNA/RNA samples prepared from the specific tissue being analyzed. The hybridization probes are purified by gel exclusion chromatography, quantitated, and hybridized with the array filters in hybridization bottles at 65°C overnight. The filters are washed under stringent conditions and signals are captured using a Fuji phosphorimager.

Data is extracted using AIS software and following background subtraction, signal normalization is performed. This includes a normalization of filter-wide expression levels between different experimental runs. Genes that are differentially expressed in the tissue of interest are identified and the full length sequence of these clones is generated.

#### ***Example 4: Chromosomal Mapping of the Polynucleotides***

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

#### ***Example 5: Bacterial Expression of a Polypeptide***

A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial

expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Ampr), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

5       The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kanr). Transformants are identified by their ability to  
10   grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical  
15   density 600 (O.D.<sup>600</sup>) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar  
20   Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

25       Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered  
30   saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500

2065

mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl.

5 The purified protein is stored at 4° C or frozen at -80° C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase  
10 gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI,  
15 BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated  
20 according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

### ***Example 6: Purification of a Polypeptide from an Inclusion Body***

25

The following alternative method can be used to purify a polypeptide expressed in *E. coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture  
30 is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by

weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH

6.5. Fractions are collected under constant  $A_{280}$  monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from

5 Commassie blue stained 16% SDS-PAGE gel when 5  $\mu$ g of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

### ***Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System***

10 In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides

20 by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion

25 and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon, is amplified using the PCR protocol described in Example 1. If a naturally occurring signal sequence is used to produce a colon or colon cancer related

30 polypeptide, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and



Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with  
5 appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

10 The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the  
15 cloned fragment is confirmed by DNA sequencing.

Five  $\mu$ g of a plasmid containing the polynucleotide is co-transfected with 1.0  $\mu$ g of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One  $\mu$ g of BaculoGold™ virus DNA and 5  $\mu$ g  
20 of the plasmid are mixed in a sterile well of a microtiter plate containing 50  $\mu$ l of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10  $\mu$ l Lipofectin plus 90  $\mu$ l Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum.  
25 The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies  
30 Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by

Life Technologies Inc., Gaithersburg, page 9- 10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200  $\mu$ l of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5  $\mu$ Ci of  $^{35}$ S-methionine and 5  $\mu$ Ci  $^{35}$ S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

### ***Example 8: Expression of a Polypeptide in Mammalian Cells***

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV1, HIV1 and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and

pCMVSPORT 3.0. Mammalian host cells that could be used include, human HeLa, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphatase by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If a naturally occurring signal sequence is used to produce the colon or colon cancer related polypeptide, the vector does not need a second signal peptide.

Alternatively, if a naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with  
5 appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction  
10 enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five  $\mu$ g of the expression plasmid pC6 or pC4 is cotransfected with 0.5  $\mu$ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a  
15 group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different  
20 concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1  $\mu$ M, 2  $\mu$ M, 5  $\mu$ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200  $\mu$ M. Expression of the desired gene product is analyzed, for  
25 instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

### ***Example 9: Protein Fusions***

The polypeptides of the present invention are preferably fused to other proteins.  
30 These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al.,

Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the half-life time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the colon or colon cancer related polypeptide, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

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GGGATCCGGAGCCCAAATCTTCTGACAAAACCTCACACATGCCCACCGTGCCCAG
CACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCAAACCCAAGGA
CACCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGTGGACGTAAGC
CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCAT
AATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTC
AGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGCCCTCCCAACCCCCATCGAGAAAACCATCTCCAAAGCC
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AAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAG  
CTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGC  
GACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGAC  
CACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACC  
5 GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCAT  
GAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAT  
GAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:8555)

***Example 10: Production of an Antibody from a Polypeptide***

10

**a) Hybridoma Technology**

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing polypeptide of the present invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of polypeptide of the present invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

Monoclonal antibodies specific for polypeptide of the present invention are prepared using hybridoma technology. (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with polypeptide of the present invention or, more preferably, with a secreted polypeptide of the present invention-expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available

from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide of the present invention.

Alternatively, additional antibodies capable of binding to polypeptide of the present invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide of the present invention-specific antibody can be blocked by polypeptide of the present invention. Such antibodies comprise anti-idiotypic antibodies to the polypeptide of the present invention-specific antibody and are used to immunize an animal to induce formation of further polypeptide of the present invention-specific antibodies.

For in vivo use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

#### **b) Isolation Of Antibody Fragments Directed Against Polypeptide of the Present Invention From A Library Of scFvs**

Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against polypeptide of the present invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

*Rescue of the Library.* A library of scFvs is constructed from the RNA of human

PBLs as described in PCT publication WO 92/01047. To rescue phage displaying antibody fragments, approximately 10<sup>9</sup> E. coli harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 µg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to inoculate 50 ml of 2xTY-AMP-GLU, 2 x 10<sup>8</sup> TU of delta gene 3 helper (M13 delta gene III, see PCT publication WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 µg/ml ampicillin and 50 µg/ml kanamycin and grown overnight. Phage are prepared as described in PCT publication WO 92/01047.

M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 µg ampicillin/ml and 25 µg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 µm filter (Minisart NML; Sartorius) to give a final concentration of approximately 10<sup>13</sup> transducing units/ml (ampicillin-resistant clones).

*Panning of the Library.* Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 µg/ml or 10 µg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately 10<sup>13</sup> TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1%



glucose and 100 µg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

*Characterization of Binders.* Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., PCT publication WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

### ***Example 11: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide***

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C, using buffer solutions described in Sidransky et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton et al., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States

Biochemical). . Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2  
5 are nick-translated with digoxigenin deoxy-uridine 5'-triphosphate (Boehringer Mannheim), and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium  
10 iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using  
15 the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

### ***Example 12: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample***

A polypeptide of the present invention can be detected in a biological sample, and if  
25 an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal  
30 or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbound polypeptide.

5        Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbound conjugate.

10        Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

### 15                                    *Example 13: Formulation*

The invention also provides methods of treatment and/or prevention of diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed herein) by administration to a subject of an effective amount of a Therapeutic. By  
20        therapeutic is meant a polynucleotides or polypeptides of the invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

The Therapeutic will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the  
25        side effects of treatment with the Therapeutic alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of the Therapeutic administered parenterally per dose will be in the range of about 1ug/kg/day to 10  
30        mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given

continuously, the Therapeutic is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Therapeutics can be administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., Id.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

Sustained-release Therapeutics also include liposomally entrapped Therapeutics of the invention (*see generally*, Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the  
5 Therapeutic are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. (USA) 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci.(USA) 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid  
10 content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal Therapeutic.

In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a pump (*see* Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)).

15 Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

For parenteral administration, in one embodiment, the Therapeutic is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that  
20 is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the Therapeutic.

Generally, the formulations are prepared by contacting the Therapeutic uniformly and  
25 intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

30 The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate,

succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The Therapeutic is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any pharmaceutical used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutics generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Therapeutics ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the Therapeutics may be employed in conjunction with other therapeutic compounds.

The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention

include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG, and MPL. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21.

5 Further adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, 10 varicella, tetanus/diphtheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are 15 administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

The Therapeutics of the invention may be administered alone or in combination with 20 other therapeutic agents. Therapeutic agents that may be administered in combination with the Therapeutics of the invention, include but not limited to, other members of the TNF family, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, cytokines and/or growth factors. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or 25 concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

30 In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited

to, soluble forms of TNF-alpha, lymphotoxin- alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha  
5 (International Publication No. WO 98/07880), TR6 (International Publication No. WO 98/30694), OPG, and neutrokin-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-1BB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International  
10 Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In certain embodiments, Therapeutics of the invention are administered in combination with  
15 antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors. Nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and  
20 COMBIVIR™ (zidovudine/lamivudine). Non-nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIVAN™ (indinavir),  
25 NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

30 In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not



limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the

Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the  
5 Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamthoxazole, and vancomycin.

10 Conventional nonspecific immunosuppressive agents, that may be administered in combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.

15 In specific embodiments, Therapeutics of the invention are administered in combination with immunosuppressants. Immunosuppressants preparations that may be administered with the Therapeutics of the invention include, but are not limited to, ORTHOCLONE™ (OKT3), SANDIMMUNE™/NEORAL™/SANGDYA™ (cyclosporin), PROGRAF™ (tacrolimus), CELLCEPT™ (mycophenolate), Azathioprine, glucorticosteroids,  
20 and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the  
25 invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, and GAMIMUNE™. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

30 In an additional embodiment, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, glucocorticoids and the nonsteroidal anti-inflammatories, aminoarylcarboxylic acid

derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

In another embodiment, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the Therapeutics of the invention include, but are not limited to, antibiotic derivatives (e.g., doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens (e.g., tamoxifen); antimetabolites (e.g., fluorouracil, 5-FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine); cytotoxic agents (e.g., carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephallen, chorambucil, mechlorethamine (nitrogen mustard) and thiotepa); steroids and combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and etoposide).

In a specific embodiment, Therapeutics of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or any combination of the components of CHOP. In another embodiment, Therapeutics of the invention are administered in combination with Rituximab. In a further embodiment, Therapeutics of the invention are administered with Rituxmab and CHOP, or Rituxmab and any combination of the components of CHOP.

In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not

limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL- 4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PlGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PlGF-2), as disclosed in Hauser et al., Growth Factors, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are incorporated herein by reference herein.

In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention include, but are not limited to, LEUKINE™ (SARGRAMOSTIM™) and NEUPOGEN™ (FILGRASTIM™).

In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

5       ***Example 14: Method of Treating Decreased Levels of the Polypeptide***

The present invention relates to a method for treating an individual in need of an increased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an agonist  
10 of the invention (including polypeptides of the invention). Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of a colon or colon cancer related polypeptide in an individual can be treated by administering the agonist or antagonist of the present invention. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising  
15 administering to such an individual a Therapeutic comprising an amount of the agonist or antagonist to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the agonist or antagonist for six consecutive days. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 13.

20

***Example 15: Method of Treating Increased Levels of the Polypeptide***

The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to  
25 such an individual a composition comprising a therapeutically effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

In one example, antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, due to a variety of etiologies, such as cancer.

30 For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day

for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 13.

***Example 16: Method of Treatment Using Gene Therapy-Ex Vivo***

5

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately  
10 ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

15 At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII  
20 and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if  
25 necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then  
30 plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

2090

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce  
5 infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer  
10 cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his.  
15 Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

### ***Example 17: Gene Therapy Using Endogenous Genes Corresponding To Polynucleotides of the Invention***

Another method of gene therapy according to the present invention involves operably associating the endogenous polynucleotide sequence of the invention with a promoter via  
25 homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA*, 86:8932-8935 (1989); and Zijlstra et al., *Nature*, 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is  
30 not expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of endogenous

polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains  
5 distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

The amplified promoter and the amplified targeting sequences are digested with the  
10 appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol precipitation.

15 In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are known in the art.

Once the cells are transfected, homologous recombination will take place which  
20 results in the promoter being operably linked to the endogenous polynucleotide sequence. This results in the expression of polynucleotide corresponding to the polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed  
25 in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na<sub>2</sub>  
30 HPO<sub>4</sub>, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin.



The final cell suspension contains approximately  $3 \times 10^6$  cells/ml. Electroporation should be performed immediately following resuspension.

Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3' end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a HindIII site at the 5' end and an XbaI site at the 3' end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5' end and a HindIII site at the 3' end. The CMV promoter and the fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least  $120 \mu\text{g/ml}$ . 0.5 ml of the cell suspension (containing approximately  $1.5 \times 10^6$  cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at  $960 \mu\text{F}$  and 250-300 V, respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

### ***Example 18: Method of Treatment Using Gene Therapy - In Vivo***

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus,

heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal

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injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

### *Example 19: Transgenic Animals*

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, e.g., baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (i.e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989));

electroporation of cells or embryos (Lo, 1983, Mol Cell Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration

of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

### ***Example 20: Knock-Out Animals***

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., *Nature* 317:230-234 (1985); Thomas & Capecchi, *Cell* 51:503-512 (1987); Thompson et al., *Cell* 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect

cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (*e.g.*, see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (*e.g.*, knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (*i.e.*, animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (*e.g.*, lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, *e.g.*, by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, *e.g.*, in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, *e.g.*, genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

### ***Example 21: Assays Detecting Stimulation or Inhibition of B cell Proliferation and Differentiation***

Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may impart a positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15. Interestingly, these signals are by themselves weak effectors but can, in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the



detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

**In Vitro Assay-** Agonists or antagonists of the invention can be assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death in B-cell populations and their precursors. The activity of the agonists or antagonists of the invention on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in the presence of either formalin-fixed *Staphylococcus aureus* Cowan 1 (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be readily identified using this assay. The assay involves isolating human tonsillar B cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220).

Various dilutions of each sample are placed into individual wells of a 96-well plate to which are added  $10^5$  B-cells suspended in culture medium (RPMI 1640 containing 10% FBS,  $5 \times 10^{-5}$ M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and  $10^{-5}$  dilution of SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well) with  $^3$ H-thymidine (6.7 Ci/mM) beginning 72h post factor addition. The positive and negative controls are IL2 and medium respectively.

**In Vivo Assay-** BALB/c mice are injected (i.p.) twice per day with buffer only, or 2 mg/Kg of agonists or antagonists of the invention, or truncated forms thereof. Mice receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with agonists or antagonists of the invention identify the results of the activity of the agonists or antagonists on spleen cells, such as the diffusion of peri-arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell representation within loosely defined B-cell zones that infiltrate established T-cell regions.

Flow cytometric analyses of the spleens from mice treated with agonist or antagonist is used to indicate whether the agonists or antagonists specifically increases the proportion of ThB+, CD45R(B220)dull B cells over that which is observed in control mice.

Likewise, a predicted consequence of increased mature B-cell representation in vivo is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared between buffer and agonists or antagonists-treated mice.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

### ***Example 22: T Cell Proliferation Assay***

A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of <sup>3</sup>H-thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 µl/well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control mAb (B33.1) overnight at 4 degrees C (1 µg/ml in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by F/H gradient centrifugation from human peripheral blood and added to quadruplicate wells (5 x 10<sup>4</sup>/well) of mAb coated plates in RPMI containing 10% FCS and P/S in the presence of varying concentrations of agonists or antagonists of the invention (total volume 200 µl). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37 degrees C, plates are spun for 2 min. at 1000 rpm and 100 µl of supernatant is removed and stored -20 degrees C for measurement of IL-2 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100 µl of medium containing 0.5 µCi of <sup>3</sup>H-thymidine and cultured at 37 degrees C for 18-24 hr. Wells are harvested and incorporation of <sup>3</sup>H-thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative controls for the effects of agonists or antagonists of the invention.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

***Example 23: Effect of Agonists or Antagonists of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells***

Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF- $\alpha$ , causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FC $\gamma$ RII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

FACS analysis of surface antigens is performed as follows. Cells are treated 1-3 days with increasing concentrations of agonist or antagonist of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

Effect on the production of cytokines. Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune responses. IL-12 strongly influences the development of Th1 helper T-cell immune response, and induces cytotoxic T and NK cell function. An ELISA is used to measure the IL-12 release as follows. Dendritic cells ( $10^6$ /ml) are treated with increasing concentrations of agonists or antagonists of the invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell cultures are then collected and analyzed for IL-12 content using commercial ELISA kit (e.g., R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

Effect on the expression of MHC Class II, costimulatory and adhesion molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules, molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the antigen presenting capacity of monocytes and ability to induce T cell activation. Increase expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of agonists or antagonists of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degreesC. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

Monocyte activation and/or increased survival. Assays for molecules that activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be applied to determine whether a molecule of the invention functions as an inhibitor or activator of monocytes. Agonists or antagonists of the invention can be screened using the three assays described below. For each of these assays, Peripheral blood mononuclear cells (PBMC) are purified from single donor leukopacks (American Red Cross, Baltimore, MD) by centrifugation through a Histopaque gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.

Monocyte Survival Assay. Human peripheral blood monocytes progressively lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated process (apoptosis). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in polypropylene tubes in serum-free medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the compound to be tested. Cells are suspended at a concentration of  $2 \times 10^6$ /ml in PBS containing PI at a

final concentration of 5 µg/ml, and then incubated at room temperature for 5 minutes before FACScan analysis. PI uptake has been demonstrated to correlate with DNA fragmentation in this experimental paradigm.

- 5 Effect on cytokine release. An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is performed as follows. Human monocytes are incubated at a density of  $5 \times 10^5$  cells/ml with increasing concentrations of agonists or antagonists of the invention and under the same conditions, but  
10 in the absence of agonists or antagonists. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in presence of agonist or antagonist of the invention. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h and kept frozen until use. Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e. g, R & D Systems (Minneapolis, MN)) and applying the standard  
15 protocols provided with the kit.

- Oxidative burst. Purified monocytes are plated in 96-w plate at  $2 \times 10^5$  cell/well. Increasing concentrations of agonists or antagonists of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10% FCS, glutamine and antibiotics). After  
20 3 days incubation, the plates are centrifuged and the medium is removed from the wells. To the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM PMA). The plates are incubated at 37°C for 2 hours and the reaction is stopped by adding 20 µl 1N NaOH per well. The  
25 absorbance is read at 610 nm. To calculate the amount of  $H_2O_2$  produced by the macrophages, a standard curve of a  $H_2O_2$  solution of known molarity is performed for each experiment.

- The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test  
30 the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

***Example 24: Biological Effects of Agonists or Antagonists of the  
Invention***

Astrocyte and Neuronal Assays.

5 Agonists or antagonists of the invention, expressed in *Escherichia coli* and purified as described above, can be tested for activity in promoting the survival, neurite outgrowth, or phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for the bioassay is based on the prevalent expression of FGF-1 and FGF-2 in cortical structures  
10 and on the previously reported enhancement of cortical neuronal survival resulting from FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate an agonist or antagonist of the invention's activity on these cells.

Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron survival  
15 and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension." *Proc. Natl. Acad. Sci. USA* 83:3012-3016. (1986), assay herein incorporated by reference in its entirety). However, reports from experiments done on PC-12 cells suggest that these two responses are not necessarily synonymous and may depend on not only which FGF is being tested but also on  
20 which receptor(s) are expressed on the target cells. Using the primary cortical neuronal culture paradigm, the ability of an agonist or antagonist of the invention to induce neurite outgrowth can be compared to the response achieved with FGF-2 using, for example, a thymidine incorporation assay.

25 Fibroblast and endothelial cell assays.

Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained in growth media from Clonetics. Dermal microvascular endothelial cells are obtained from Cell Applications (San Diego, CA). For proliferation assays, the human lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate  
30 for one day in growth medium. The cells are then incubated for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is

added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the PGE<sub>2</sub> assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or agonists or antagonists of the invention with or without IL-1 $\alpha$  for 24 hours. The supernatants are collected and assayed for PGE<sub>2</sub> by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without agonists or antagonists of the invention IL-1 $\alpha$  for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

Human lung fibroblasts are cultured with FGF-2 or agonists or antagonists of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on growth of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with agonists or antagonists of the invention.

#### Parkinson Models.

The loss of motor function in Parkinson's disease is attributed to a deficiency of striatal dopamine resulting from the degeneration of the nigrostriatal dopaminergic projection neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine (MPP<sup>+</sup>) and released. Subsequently, MPP<sup>+</sup> is actively accumulated in dopaminergic neurons by the high-affinity reuptake transporter for dopamine. MPP<sup>+</sup> is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotinamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J. Neuroscience, 1990).

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Based on the data with FGF-2, agonists or antagonists of the invention can be evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival *in vitro* and it can also be tested *in vivo* for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential effect of an agonist or antagonist of the invention is first examined *in vitro* in a dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/cm<sup>2</sup> on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium containing hormonal supplements (N1). The cultures are fixed with paraformaldehyde after 8 days *in vitro* and are processed for tyrosine hydroxylase, a specific marker for dopaminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

Since the dopaminergic neurons are isolated from animals at gestation day 14, a developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive neurons would represent an increase in the number of dopaminergic neurons surviving *in vitro*. Therefore, if an agonist or antagonist of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the agonist or antagonist may be involved in Parkinson's Disease.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

### ***Example 25: The Effect of Agonists or Antagonists of the Invention on the Growth of Vascular Endothelial Cells***

On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at  $2-5 \times 10^4$  cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnology,



Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. An agonist or antagonist of the invention, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

5 An increase in the number of HUVEC cells indicates that the compound of the invention may proliferate vascular endothelial cells, while a decrease in the number of HUVEC cell indicates that the compound of the invention inhibits vascular endothelial cells.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity  
10 of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

### ***Example 26: Rat Corneal Wound Healing Model***

This animal model shows the effect of an agonist or antagonist of the invention on  
15 neovascularization. The experimental protocol includes:

- a) Making a 1-1.5 mm long incision from the center of cornea into the stromal layer.
- b) Inserting a spatula below the lip of the incision facing the outer corner of the eye.
- 20 c) Making a pocket (its base is 1-1.5 mm from the edge of the eye).
- d) Positioning a pellet, containing 50ng- 5ug of an agonist or antagonist of the invention, within the pocket.
- e) Treatment with an agonist or antagonist of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg - 500mg (daily treatment for five  
25 days).

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

### ***Example 27: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models***

**A. Diabetic db+/db+ Mouse Model.**

To demonstrate that an agonist or antagonist of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner, M.H. *et al.*, *J. Surg. Res.* 52:389 (1992); Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)).

The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single autosomal recessive mutation on chromosome 4 (db+) (Coleman *et al.* *Proc. Natl. Acad. Sci. USA* 77:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin levels, and suppressed cell-mediated immunity (Mandel *et al.*, *J. Immunol.* 120:1375 (1978); Debray-Sachs, M. *et al.*, *Clin. Exp. Immunol.* 51(1):1-7 (1983); Leiter *et al.*, *Am. J. of Pathol.* 114:46-55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. *et al.*, *Exp. Neurol.* 83(2):221-232 (1984); Robertson *et al.*, *Diabetes* 29(1):60-67 (1980); Giacomelli *et al.*, *Lab Invest.* 40(4):460-473 (1979); Coleman, D.L., *Diabetes* 31 (Suppl):1-6 (1982)). These homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel *et al.*, *J. Immunol.* 120:1375-1377 (1978)).

The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, *et al.*, *Am. J. of Pathol.* 136:1235-1246 (1990)).

Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the

rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., *J. Exp. Med.* 172:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

An agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm<sup>2</sup>, the corresponding size of the dermal punch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned  
5 perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome.  
Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected  
wounds. Histologic examination of the wounds are used to assess whether the healing  
process and the morphologic appearance of the repaired skin is altered by treatment with an  
agonist or antagonist of the invention. This assessment included verification of the presence  
10 of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-epithelialization and  
epidermal maturity (Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)). A calibrated  
lens micrometer is used by a blinded observer.

Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human  
keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue  
15 control while non-immune IgG is used as a negative control. Keratinocyte growth is  
determined by evaluating the extent of reepithelialization of the wound using a calibrated  
lens micrometer.

Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated  
by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon  
20 cancer served as a positive tissue control and human brain tissue is used as a negative tissue  
control. Each specimen included a section with omission of the primary antibody and  
substitution with non-immune mouse IgG. Ranking of these sections is based on the extent  
of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to  
the higher side reflecting intense proliferation.

25 Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is  
considered significant.

#### *B. Steroid Impaired Rat Model*

The inhibition of wound healing by steroids has been well documented in various *in*  
30 *vitro* and *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-Inflammatory  
Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahlet *et al.*, *J. Immunol.* 115:  
476-481 (1975); Werb *et al.*, *J. Exp. Med.* 147:1684-1694 (1978)). Glucocorticoids retard

wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert *et al.*, *An. Intern. Med.* 37:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck *et al.*, *Growth Factors*. 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", *In: Antiinflammatory Steroid Action: Basic and Clinical Aspects*, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish phenomenon in rats (Beck *et al.*, *Growth Factors*. 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", *In: Antiinflammatory Steroid Action: Basic and Clinical Aspects*, Academic Press, New York, pp. 280-302 (1989); Pierce *et al.*, *Proc. Natl. Acad. Sci. USA* 86: 2229-2233 (1989)).

To demonstrate that an agonist or antagonist of the invention can accelerate the healing process, the effects of multiple topical applications of the agonist or antagonist on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and are 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad libitum*. All manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

The wounding protocol is followed according to section A, above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue punch. The wounds are left open for the duration of the experiment. Applications of the testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

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Wounds are visually examined and photographed at a fixed distance at the day of wounding and at the end of treatment. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

The agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Four groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total area of the wound. Closure is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm<sup>2</sup>, the corresponding size of the dermal punch. Calculations are made using the following formula:

$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds allows assessment of whether the healing process and the morphologic appearance of the repaired skin is improved by treatment with an agonist or antagonist of the invention. A calibrated lens micrometer is used by a blinded observer to determine the distance of the wound gap.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

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### *Example 28: Lymphadema Animal Model*

The purpose of this experimental approach is to create an appropriate and consistent lymphedema model for testing the therapeutic effects of an agonist or antagonist of the invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system in the rat hind limb. Effectiveness is measured by swelling volume of the affected limb, quantification of the amount of lymphatic vasculature, total blood plasma protein, and histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly, the chronic progress of the edema is followed for up to 3-4 weeks.

15 Prior to beginning surgery, blood sample is drawn for protein concentration analysis. Male rats weighing approximately ~350g are dosed with Pentobarbital. Subsequently, the right legs are shaved from knee to hip. The shaved area is swabbed with gauze soaked in 70% EtOH. Blood is drawn for serum total protein testing. Circumference and volumetric measurements are made prior to injecting dye into paws after marking 2 measurement levels  
20 (0.5 cm above heel, at mid-pt of dorsal paw). The intradermal dorsum of both right and left paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric measurements are then made following injection of dye into paws.

Using the knee joint as a landmark, a mid-leg inguinal incision is made circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used  
25 to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel that runs along side and underneath the vessel(s) is located. The main lymphatic vessels in this area are then electrically coagulated or suture ligated.

Using a microscope, muscles in back of the leg (near the semitendinosus and adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal  
30 and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then and ligated by suturing. The popliteal lymph node, and any accompanying adipose tissue, is then removed by cutting connective tissues.

Care is taken to control any mild bleeding resulting from this procedure. After lymphatics are occluded, the skin flaps are sealed by using liquid skin (Vetbond) (AJ Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying muscle when  
5 necessary.

To avoid infection, animals are housed individually with mesh (no bedding). Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the intensity of the lymphedema, the circumference and volumes of 2 designated places on each  
10 paw before operation and daily for 7 days are measured. The effect plasma proteins on lymphedema is determined and whether protein analysis is a useful testing perimeter is also investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

Circumference Measurements: Under brief gas anesthetic to prevent limb movement,  
15 a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people then those 2 readings are averaged. Readings are taken from both control and edematous limbs.

Volumetric Measurements: On the day of surgery, animals are anesthetized with Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under brief  
20 halothane anesthetic (rapid immobilization and quick recovery), both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in water, then dipped into instrument to each marked level then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the limb to marked area.

Blood-plasma protein measurements: Blood is drawn, spun, and serum separated  
25 prior to surgery and then at conclusion for total protein and Ca<sup>2+</sup> comparison.

Limb Weight Comparison: After drawing blood, the animal is prepared for tissue collection. The limbs are amputated using a quillitine, then both experimental and control legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

30 Histological Preparations: The transverse muscle located behind the knee (popliteal) area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold



methylbutane, placed into labeled sample bags at - 80°C until sectioning. Upon sectioning, the muscle is observed under fluorescent microscopy for lymphatics..

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

***Example 29: Suppression of TNF alpha-induced adhesion molecule expression by a Agonist or Antagonist of the Invention***

The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Tumor necrosis factor alpha (TNF- $\alpha$ ), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

The potential of an agonist or antagonist of the invention to mediate a suppression of TNF- $\alpha$  induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF- $\alpha$  treated ECs when co-stimulated with a member of the FGF family of proteins.

To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% CO<sub>2</sub>. HUVECs are seeded in 96-well plates at concentrations of  $1 \times 10^4$  cells/well in EGM medium at 37 degree C for 18-24 hrs or until confluent. The monolayers are subsequently washed 3 times with a serum-free solution

of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following incubation, the cells are then evaluated for CAM expression.

Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well plate to confluence. Growth medium is removed from the cells and replaced with 90 ul of 199 Medium (10% FBS). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 ul volumes). Plates are incubated at 37 degree C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 µl of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min.

Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10 µl of diluted primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 µg/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

Then add 20 µl of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution) to each well and incubated at 37°C for 30 min. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH 10.4). 100 µl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphatase in glycine buffer:  $1:5,000 (10^0) > 10^{-0.5} > 10^{-1} > 10^{-1.5}$ . 5 µl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 µl of pNPP reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50 µl of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on blank wells filled with glycine buffer only. The template is set up to indicate the concentration of AP-conjugate in each standard well [ 5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

### ***Example 30: TAQMAN***

Quantitative PCR (QPCR). Total RNA from cells in culture are extracted by Trizol  
5 separation as recommended by the supplier (LifeTechnologies). (Total RNA is treated with  
DNase I (Life Technologies) to remove any contaminating genomic DNA before reverse  
transcription.) Total RNA (50 ng) is used in a one-step, 50ul, RT-QPCR, consisting of  
Taqman Buffer A (Perkin-Elmer; 50 mM KCl/10 mM Tris, pH 8.3), 5.5 mM MgCl<sub>2</sub>, 240 µM  
each dNTP, 0.4 units RNase inhibitor(Promega), 8%glycerol, 0.012% Tween-20, 0.05%  
10 gelatin, 0.3uM primers, 0.1uM probe, 0.025units Amplitaq Gold (Perkin-Elmer) and 2.5 units  
Superscript II reverse transcriptase (Life Technologies). As a control for genomic  
contamination, parallel reactions are setup without reverse transcriptase. The relative  
abundance of (unknown) and 18S RNAs are assessed by using the Applied Biosystems Prism  
7700 Sequence Detection System (Livak, K. J., Flood, S. J., Marmaro, J., Giusti, W. &  
15 Deetz, K. (1995) PCR Methods Appl. 4, 357-362). Reactions are carried out at 48°C for 30  
min, 95°C for 10 min, followed by 40 cycles of 95°C for 15s, 60°C for 1 min. Reactions are  
performed in triplicate.

Primers (f & r) and FRET probes sets are designed using Primer Express Software  
(Perkin-Elmer). Probes are labeled at the 5'-end with the reporter dye 6-FAM and on the 3'-  
20 end with the quencher dye TAMRA (Biosource International, Camarillo, CA or Perkin-  
Elmer).

### ***Example 31: Production Of Polypeptide of the Invention For High- Throughput Screening Assays***

25

The following protocol produces a supernatant containing polypeptide of the present  
invention to be tested. This supernatant can then be used in the Screening Assays described  
in Examples 33-42.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml  
30 in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working  
solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at  
RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel

pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

- 5           Plate 293T cells (do not carry cells past P+20) at  $2 \times 10^5$  cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

- The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8-10, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix.
- 10           Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

- Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37 degree C for 6 hours.
- 20           While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or HGS CHO-5 media (116.6 mg/L of  $\text{CaCl}_2$  (anhyd); 0.00130 mg/L  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ; 0.050 mg/L of  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ ; 0.417 mg/L of  $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ ; 311.80 mg/L of Kcl; 28.64 mg/L of  $\text{MgCl}_2$ ; 48.84 mg/L of  $\text{MgSO}_4$ ; 6995.50 mg/L of NaCl; 2400.0 mg/L of  $\text{NaHCO}_3$ ; 62.50 mg/L of  $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ ; 71.02 mg/L of  $\text{Na}_2\text{HPO}_4$ ; .4320 mg/L of  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ ; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L

- 25           While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or HGS CHO-5 media (116.6 mg/L of  $\text{CaCl}_2$  (anhyd); 0.00130 mg/L  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ; 0.050 mg/L of  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ ; 0.417 mg/L of  $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ ; 311.80 mg/L of Kcl; 28.64 mg/L of  $\text{MgCl}_2$ ; 48.84 mg/L of  $\text{MgSO}_4$ ; 6995.50 mg/L of NaCl; 2400.0 mg/L of  $\text{NaHCO}_3$ ; 62.50 mg/L of  $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ ; 71.02 mg/L of  $\text{Na}_2\text{HPO}_4$ ; .4320 mg/L of  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ ; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L
- 30           While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or HGS CHO-5 media (116.6 mg/L of  $\text{CaCl}_2$  (anhyd); 0.00130 mg/L  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ; 0.050 mg/L of  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ ; 0.417 mg/L of  $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ ; 311.80 mg/L of Kcl; 28.64 mg/L of  $\text{MgCl}_2$ ; 48.84 mg/L of  $\text{MgSO}_4$ ; 6995.50 mg/L of NaCl; 2400.0 mg/L of  $\text{NaHCO}_3$ ; 62.50 mg/L of  $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ ; 71.02 mg/L of  $\text{Na}_2\text{HPO}_4$ ; .4320 mg/L of  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ ; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L

of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L- Arginine-HCL; 7.50 mg/ml of L-Asparagine-H<sub>2</sub>O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H<sub>2</sub>O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-  
5 Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L- Histidine-HCL-H<sub>2</sub>O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H<sub>2</sub>O; and 99.65 mg/ml of L-  
10 Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; 0.680 mg/L of Vitamin B12; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of  
15 Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal Acetate. Adjust osmolarity to 327 mOsm) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer)  
20 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37 degree C for 45 or 72 hours depending on the  
25 media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 33-40.

It is specifically understood that when activity is obtained in any of the assays  
30 described below using a supernatant, the activity originates from either the polypeptide of the present invention directly (e.g., as a secreted protein) or by polypeptide of the present invention inducing expression of other proteins, which are then secreted into the supernatant.

Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

### *Example 32: Construction of GAS Reporter Construct*

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One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements  
10 alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has  
15 been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks  
20 represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A  
25 cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding  
30 Trp-Ser-Xxx-Trp-Ser (SEQ ID NO: 8556)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is

encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter  
5 molecules, activators of the Jaks-STATs pathway can be identified.

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	<u>Ligand</u>	<u>tyk2</u>	<u>JAKs</u>			<u>STATs GAS(elements) or ISRE</u>	
			<u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>		
	<u>IFN family</u>						
5	IFN-a/B	+	+	-	-	1,2,3	ISRE
	IFN-g		+	+	-	1	GAS
	(IRF1>Lys6>IFP)						
	IL-10	+	?	?	-	1,3	
10	<u>gp130 family</u>						
	IL-6 (Pleiotrohic)	+	+	+	?	1,3	GAS
	(IRF1>Lys6>IFP)						
	IL-11(Pleiotrohic)	?	+	?	?	1,3	
	OnM(Pleiotrohic)	?	+	+	?	1,3	
15	LIF(Pleiotrohic)	?	+	+	?	1,3	
	CNTF(Pleiotrohic)	-/+	+	+	?	1,3	
	G-CSF(Pleiotrohic)	?	+	?	?	1,3	
	IL-12(Pleiotrohic)	+	-	+	+	1,3	
20	<u>g-C family</u>						
	IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
	IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP
	>>Ly6)(IgH)						
	IL-7 (lymphocytes)	-	+	-	+	5	GAS
25	IL-9 (lymphocytes)	-	+	-	+	5	GAS
	IL-13 (lymphocyte)	-	+	?	?	6	GAS
	IL-15	?	+	?	+	5	GAS
	<u>gp140 family</u>						
30	IL-3 (myeloid)	-	-	+	-	5	GAS
	(IRF1>IFP>>Ly6)						
	IL-5 (myeloid)	-	-	+	-	5	GAS
	GM-CSF (myeloid)	-	-	+	-	5	GAS



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Growth hormone family

	GH	?	-	+	-	5	
	PRL	?	+/-	+	-	1,3,5	
5	EPO	?	-	+	-	5	GAS(B-
	CAS>IRF1=IFP>>Ly6)						

Receptor Tyrosine Kinases

	EGF	?	+	+	-	1,3	GAS (IRF1)
10	PDGF	?	+	+	-	1,3	
	CSF-1	?	+	+	-	1,3	GAS (not IRF1)

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 33-34, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAAT  
10 GATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:8557)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:8558)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATT  
TCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACT  
CCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTG  
20 ACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCC  
AGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAAGCTT:3'  
(SEQ ID NO:8559)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

30 The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the

GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and  
5 NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 33-34.

Other constructs can be made using the above description and replacing GAS with a  
10 different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 35 and 36. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly,  
15 other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

### ***Example 33: High-Throughput Screening Assay for T-cell Activity.***

The following protocol is used to assess T-cell activity by identifying factors, and  
20 determining whether supernate containing a polypeptide of the invention proliferates and/or differentiates T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 32. Thus, factors that increase SEAP activity indicate the ability to  
25 activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable  
30 cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then

tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient  
5 cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required  
10 number of cells ( $10^7$  per transfection), and resuspend in OPTI-MEM to a final concentration of  $10^7$  cells/ml. Then add 1ml of  $1 \times 10^7$  cells in OPTI-MEM to T25 flask and incubate at 37 degree C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Genticin, and 1% Pen-Strep. These cells are treated with supernatants containing  
15 polypeptide of the present invention or polypeptide of the present invention induced polypeptides as produced by the protocol described in Example 31.

On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one  
20 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred directly  
25 from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each  
30 well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20 degree C until SEAP assays are performed according to Example 37. The plates containing the remaining treated

cells are placed at 4 degree C and serve as a source of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

***Example 34: High-Throughput Screening Assay Identifying Myeloid Activity.***

The following protocol is used to assess myeloid activity of polypeptide of the present invention by determining whether polypeptide of the present invention proliferates and/or differentiates myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 32. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 32, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest  $2 \times 10^7$  U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ , 1 mM  $\text{MgCl}_2$ , and 675 uM  $\text{CaCl}_2$ . Incubate at 37 degrees C for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degree C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting  $1 \times 10^8$  cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium,

with a final density of  $5 \times 10^5$  cells/ml. Plate 200  $\mu$ l cells per well in the 96-well plate (or  $1 \times 10^5$  cells/well).

Add 50  $\mu$ l of the supernatant prepared by the protocol described in Example 31. Incubate at 37 degree C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 37.

### *Example 35: High-Throughput Screening Assay Identifying Neuronal Activity.*

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed by polypeptide of the present invention.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells by polypeptide of the present invention can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO: 8560)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO: 8561)

Using the GAS:SEAP/Neo vector produced in Example 32, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified

product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 31. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as  $5 \times 10^5$  cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to  $1 \times 10^5$  cells/well). Add 50 ul supernatant produced by Example 31, 37 degree C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 37.

### ***Example 36: High-Throughput Screening Assay for T-cell Activity.***

NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide variety of

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agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded, causing NF- KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the supernatants produced in Example 31. Activators or inhibitors of NF-KB would be useful in treating, preventing, and/or diagnosing diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid arthritis.

To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-KB binding site (GGGGACTTTCCC) (SEQ ID NO:8562), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTC  
CATCCTGCCATCTCAATTAG:3' (SEQ ID NO:8563)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:8558)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCCATCTG  
CCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCC  
CTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTAT  
TTATGCAGAGGCCGAGGCCGCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGG



AGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT:3' (SEQ ID NO:8564)

Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP cassette is removed from the above NF-KB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 33. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 33. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

### ***Example 37: Assay for SEAP Activity.***

As a reporter molecule for the assays described in Examples 33-36, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min.

Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the

2133

results. An increase in chemiluminescence

indicates reporter activity.

## Reaction Buffer Formulation:

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11

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43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

---

***Example 38: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability.***

5

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

10

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

15

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO<sub>2</sub> incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

20

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37 degrees C in a CO<sub>2</sub> incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

25

For non-adherent cells, the cells are spun down from culture media. Cells are resuspended to 2-5x10<sup>6</sup> cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4

solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to  $1 \times 10^6$  cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley Cell Wash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4. The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event caused by the a molecule, either polypeptide of the present invention or a molecule induced by polypeptide of the present invention, which has resulted in an increase in the intracellular  $Ca^{++}$  concentration.

#### ***Example 40: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity.***

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase

activity, identifying whether polypeptide of the present invention or a molecule induced by polypeptide of the present invention is capable of activating tyrosine kinase signal transduction pathways is of interest. Therefore, the following protocol is designed to identify such molecules capable of activating the tyrosine kinase signal transduction pathways.

5       Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which  
10       can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers  
15       #3071 from Becton Dickinson (Bedford, MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

      To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced  
20       by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 31, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na<sub>3</sub>VO<sub>4</sub>, 2 mM Na<sub>4</sub>P<sub>2</sub>O<sub>7</sub> and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate  
25       is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is  
30       removed and centrifuged for 15 minutes at 4 degree C at 16,000 x g.

      Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg<sup>2+</sup> (5mM ATP/50mM MgCl<sub>2</sub>), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl<sub>2</sub>, 5 mM MnCl<sub>2</sub>, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degree C for 2 min. Initiate the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degree C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degree C for one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

#### ***Example 41: High-Throughput Screening Assay Identifying Phosphorylation Activity.***

As a potential alternative and/or complement to the assay of protein tyrosine kinase activity described in Example 40, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as

described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degree C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyn filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 31 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation by polypeptide of the present invention or a molecule induced by polypeptide of the present invention.

#### ***Example 42: Assay for the Stimulation of Bone Marrow CD34+ Cell Proliferation.***

This assay is based on the ability of human CD34+ to proliferate in the presence of

hematopoietic growth factors and evaluates the ability of isolated polypeptides expressed in mammalian cells to stimulate proliferation of CD34+ cells.

It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond. Therefore, to test the effect of polypeptides on hematopoietic activity of a wide range of progenitor cells, the assay contains a given polypeptide in the presence or absence of other hematopoietic growth factors. Isolated cells are cultured for 5 days in the presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone has a very limited effect on the proliferation of bone marrow (BM) cells, acting in such conditions only as a "survival" factor. However, combined with any factor exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested polypeptide has a stimulatory effect on a hematopoietic progenitors, such activity can be easily detected. Since normal BM cells have a low level of cycling cells, it is likely that any inhibitory effect of a given polypeptide, or agonists or antagonists thereof, might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to *in vitro* stimulation with SCF+IL-3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

Briefly, CD34+ cells are isolated using methods known in the art. The cells are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-glutamine (500ml) Quality Biological, Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to  $2.5 \times 10^5$  cells/ml. During this time, 100  $\mu$ l of sterile water is added to the peripheral wells of a 96-well plate. The cytokines that can be tested with a given polypeptide in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, 10  $\mu$ l of prepared cytokines, 50  $\mu$ l of the supernatants prepared in Example 31 (supernatants at 1:2 dilution = 50  $\mu$ l) and 20  $\mu$ l of diluted cells are added to the media which is already present in the wells to allow for a final total volume of 100  $\mu$ l. The plates are then placed in a 37°C/5% CO<sub>2</sub> incubator for five days.

Eighteen hours before the assay is harvested, 0.5  $\mu$ Ci/well of [3H] Thymidine is added in a 10  $\mu$ l volume to each well to determine the proliferation rate. The experiment is terminated by harvesting the cells from each 96-well plate to a filtermat using the Tomtec



Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60 µl Microscint is added to each well and the plate sealed with TopSeal-A press-on sealing film. A bar code 15 sticker is affixed to the first plate for counting. The sealed plates is then loaded and the level of radioactivity determined via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

The studies described in this example test the activity of a given polypeptide to stimulate bone marrow CD34+ cell proliferation. One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, 10 agonists, and/or antagonists and fragments and variants thereof. As a nonlimiting example, potential antagonists tested in this assay would be expected to inhibit cell proliferation in the presence of cytokines and/or to increase the inhibition of cell proliferation in the presence of cytokines and a given polypeptide. In contrast, potential agonists tested in this assay would be expected to enhance cell proliferation and/or to decrease the inhibition of cell proliferation 15 in the presence of cytokines and a given polypeptide.

The ability of a gene to stimulate the proliferation of bone marrow CD34+ cells indicates that polynucleotides and polypeptides corresponding to the gene are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" 20 sections above, and elsewhere herein.

### ***Example 43: Assay for Extracellular Matrix Enhanced Cell Response (EMECR).***

25 The objective of the Extracellular Matrix Enhanced Cell Response (EMECR) assay is to identify gene products (e.g., isolated polypeptides) that act on the hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

Cells respond to the regulatory factors in the context of signal(s) received from the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem 30 cells fail to replicate in the absence of signals from the ECM. Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is dependent upon their interaction with the

stromal cells and the ECM protein fibronectin (fn). Adhesion of cells to fn is mediated by the  $\alpha_5\beta_1$  and  $\alpha_4\beta_1$  integrin receptors, which are expressed by human and mouse hematopoietic stem cells. The factor(s) which integrate with the ECM environment and responsible for stimulating stem cell self-renewal has not yet been identified. Discovery of such factors should be of great interest in gene therapy and bone marrow transplant applications

Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with fn fragment at a coating concentration of  $0.2 \mu\text{g}/\text{cm}^2$ . Mouse bone marrow cells are plated (1,000 cells/well) in 0.2 ml of serum-free medium. Cells cultured in the presence of IL-3 (5 ng/ml) + SCF (50 ng/ml) would serve as the positive control, conditions under which little self-renewal but pronounced differentiation of the stem cells is to be expected. Gene products of the invention (e.g., including, but not limited to, polynucleotides and polypeptides of the present invention, and supernatants produced in Example 31), are tested with appropriate negative controls in the presence and absence of SCF(5.0 ng/ml), where test factor supernates represent 10% of the total assay volume. The plated cells are then allowed to grow by incubating in a low oxygen environment (5%  $\text{CO}_2$ , 7%  $\text{O}_2$ , and 88%  $\text{N}_2$ ) tissue culture incubator for 7 days. The number of proliferating cells within the wells is then quantitated by measuring thymidine incorporation into cellular DNA. Verification of the positive hits in the assay will require phenotypic characterization of the cells, which can be accomplished by scaling up of the culture system and using appropriate antibody reagents against cell surface antigens and FACScan.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

If a particular polypeptide of the present invention is found to be a stimulator of hematopoietic progenitors, polynucleotides and polypeptides corresponding to the gene encoding said polypeptide may be useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein. The gene product may also be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Additionally, the polynucleotides and/or polypeptides of the gene of interest and/or

agonists and/or antagonists thereof, may also be employed to inhibit the proliferation and differentiation of hematopoietic cells and therefore may be employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

Moreover, polynucleotides and polypeptides corresponding to the gene of interest may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, for example, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

***Example 44: Human Dermal Fibroblast and Aortic Smooth Muscle Cell Proliferation.***

The polypeptide of interest is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two co-assays are performed with each sample. The first assay examines the effect of the polypeptide of interest on the proliferation of normal human dermal fibroblasts (NHDF) or aortic smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without co-TNF $\alpha$  stimulation, in order to check for costimulatory or inhibitory activity.

Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100  $\mu$ l culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin, 2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5  $\mu$ g/ml hEGF, 5mg/ml insulin, 1 $\mu$ g/ml hFGF, 50mg/ml gentamycin, 50  $\mu$ g/ml Amphotericin B, 5%FBS. After incubation at 37°C for at least 4-5 hours, culture media is aspirated and replaced with growth arrest media. Growth arrest media for NHDF contains fibroblast basal media, 50mg/ml gentamycin, 2%

FBS, while growth arrest media for AoSMC contains SM basal media, 50mg/ml gentamycin, 50µg/ml Amphotericin B, 0.4% FBS. Incubate at 37°C until day 2.

On day 2, serial dilutions and templates of the polypeptide of interest are designed such that they always include media controls and known-protein controls. For both stimulation and inhibition experiments, proteins are diluted in growth arrest media. For inhibition experiments, TNFa is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Add 1/3 vol media containing controls or polypeptides of the present invention and incubate at 37°C/5% CO<sub>2</sub> until day 5.

Transfer 60µl from each well to another labeled 96-well plate, cover with a plate-sealer, and store at 4°C until Day 6 (for IL6 ELISA). To the remaining 100 µl in the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the culture volume (10µl). Return plates to incubator for 3 to 4 hours. Then measure fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100 ul/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON at room temperature.

On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay Buffer containing PBS with 4% BSA. Block the plates with 200 µl/well of Pierce Super Block blocking buffer in PBS for 1-2 hr and then wash plates with wash buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50 µl/well of diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make dilutions of IL-6 stock in media (30, 10, 3, 1, 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker. Plates are washed with wash buffer and blotted on paper towels. Dilute EU-labeled Streptavidin 1:1000 in Assay buffer, and add 100 µl/well. Cover the plate and incubate 1 h at RT. Plates are again washed with wash buffer and blotted on paper towels. Add 100 µl/well of Enhancement Solution and shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each assay are tabulated and averaged.

A positive result in this assay suggests AoSMC cell proliferation and that the polypeptide of the present invention may be involved in dermal fibroblast proliferation and/or smooth muscle cell proliferation. A positive result also suggests many potential uses of

polypeptides, polynucleotides, agonists and/or antagonists of the polynucleotide/polypeptide of the present invention which gives a positive result. For example, inflammation and immune responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, polypeptides of the present invention and polynucleotides of the present invention may be used in wound healing and dermal regeneration, as well as the promotion of vasculogenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of, for example, cardiovascular diseases. Additionally, antagonists of polypeptides and polynucleotides of the invention may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular (e.g., anti-angiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, antagonists of polypeptides and polynucleotides of the invention may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

#### ***Example 45: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells.***

The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100  $\mu$ l of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10  $\mu$ l volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100  $\mu$ l of 0.1% paraformaldehyde-PBS(with Ca<sup>++</sup> and Mg<sup>++</sup>) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA and drained. 10  $\mu$ l of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10  $\mu$ g/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20  $\mu$ l of diluted ExtrAvidin-Alkaline Phosphotase (1:5,000 dilution, referred to herein as the working dilution) are added to each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100  $\mu$ l of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphotase in glycine buffer: 1:5,000 ( $10^0$ ) >  $10^{-0.5}$  >  $10^{-1}$  >  $10^{-1.5}$ . 5  $\mu$ l of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100  $\mu$ l of pNPP reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50  $\mu$ l of 3M NaOH is added to all wells. The plate is read on a plate reader

at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [ 5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

5

***Example 46: Alamar Blue Endothelial Cells Proliferation Assay.***

This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic  
10 Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue Proliferation Assay is prepared in EGM-2MV with 10 ng /ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration.  
15 Dilutions of the protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and Angiostatin or TSP-1 are included as a known inhibitory controls.

Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37-C overnight. After the overnight  
20 incubation of the cells, the growth media is removed and replaced with GIBCO EC-SFM. The cells are treated with the appropriate dilutions of the protein of interest or control protein sample(s) (prepared in SFM ) in triplicate wells with additional bFGF to a concentration of 10 ng/ ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37° C incubator for three days. After three days 10 ml of stock alamar blue (Biosource  
25 Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

Alamar blue is an oxidation-reduction indicator that both fluoresces and changes color  
30 in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from

oxidized (non-fluorescent blue) form to reduced (fluorescent red) form. i.e. stimulated proliferation will produce a stronger signal and inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity. The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

***Example 47: Detection of Inhibition of a Mixed Lymphocyte Reaction.***

This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides). Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

Polypeptides of interest found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM<sup>®</sup>, density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to  $2 \times 10^6$  cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to  $2 \times 10^5$  cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50  $\mu$ l) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1  $\mu$ g/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final



concentration of 10 µg/ml. Cells are cultured for 7-8 days at 37°C in 5% CO<sub>2</sub>, and 1 µC of [<sup>3</sup>H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

5        Samples of the protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

10        One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

#### *Example 48: Assays for Protease Activity.*

15        The following assay may be used to assess protease activity of the colon or colon cancer related polypeptides of the invention.

20        Gelatin and casein zymography are performed essentially as described (Heusen et al., *Anal. Biochem.*, 102:196-202 (1980); Wilson et al., *Journal of Urology*, 149:653-658 (1993)). Samples are run on 10% polyacrylamide/0.1% SDS gels containing 1% gelatin or casein, soaked in 2.5% triton at room temperature for 1 hour, and in 0.1M glycine, pH 8.3 at 37°C 5 to 16 hours. After staining in amido black areas of proteolysis appear as clear areas against the blue-black background. Trypsin (Sigma T8642) is used as a positive control.

25        Protease activity is also determined by monitoring the cleavage of n-a-benzoyl-L-arginine ethyl ester (BAEE) (Sigma B-4500. Reactions are set up in (25mM NaPO<sub>4</sub>, 1mM EDTA, and 1mM BAEE), pH 7.5. Samples are added and the change in adsorbance at 260nm is monitored on the Beckman DU-6 spectrophotometer in the time-drive mode. Trypsin is used as a positive control

30        Additional assays based upon the release of acid-soluble peptides from casein or hemoglobin measured as adsorbance at 280 nm or colorimetrically using the Folin method are performed as described in Bergmeyer, et al., *Methods of Enzymatic Analysis*, 5 (1984). Other assays involve the solubilization of chromogenic substrates (Ward, *Applied Science*, 251-317 (1983).

***Example 49: Identifying Serine Protease Substrate Specificity.***

Methods known in the art or described herein may be used to determine the substrate  
5 specificity of the polypeptides of the present invention having serine protease activity. A  
preferred method of determining substrate specificity is by the use of positional scanning  
synthetic combinatorial libraries as described in GB 2 324 529 (incorporated herein in its  
entirety).

***Example 50: Ligand Binding Assays.***

The following assay may be used to assess ligand binding activity of the colon or  
colon cancer related polypeptides of the invention.

Ligand binding assays provide a direct method for ascertaining receptor  
15 pharmacology and are adaptable to a high throughput format. The purified ligand for a colon  
or colon cancer related polypeptide is radiolabeled to high specific activity (50-2000  
Ci/mmol) for binding studies. A determination is then made that the process of radiolabeling  
does not diminish the activity of the ligand towards its colon or colon cancer related  
polypeptide. Assay conditions for buffers, ions, pH and other modulators such as nucleotides  
20 are optimized to establish a workable signal to noise ratio for both membrane and whole cell  
colon or colon cancer related polypeptide sources. For these assays, specific colon or colon  
cancer related polypeptide binding is defined as total associated radioactivity minus the  
radioactivity measured in the presence of an excess of unlabeled competing ligand. Where  
possible, more than one competing ligand is used to define residual nonspecific binding.

***Example 51: Functional Assay in *Xenopus* Oocytes.***

Capped RNA transcripts from linearized plasmid templates encoding the colon or  
colon cancer related antigen cDNAs of the invention are synthesized in vitro with RNA  
30 polymerases in accordance with standard procedures. In vitro transcripts are suspended in  
water at a final concentration of 0.2 mg/ml. Ovarian lobes are removed from adult female  
toads, Stage V defolliculated oocytes are obtained, and RNA transcripts (10 ng/oocyte) are

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injected in a 50 nl bolus using a microinjection apparatus. Two electrode voltage clamps are used to measure the currents from individual *Xenopus oocytes* in response to colon cancer antigen or colon cancer antigen agonist exposure. Recordings are made in Ca<sup>2+</sup> free Barth's medium at room temperature. The *Xenopus* system can be used to screen  
5 known ligands and tissue/cell extracts for activating ligands.

### ***Example 52: Microphysiometric Assays.***

Activation of a wide variety of secondary messenger systems results in extrusion of  
10 small amounts of acid from a cell. The acid formed is largely as a result of the increased metabolic activity required to fuel the intracellular signaling process. The pH changes in the media surrounding the cell are very small but are detectable by the CYTOSENSOR microphysiometer (Molecular Devices Ltd., Menlo Park, Calif.). The CYTOSENSOR is thus capable of detecting the activation of a colon cancer antigen which is coupled to an energy  
15 utilizing intracellular signaling pathway.

### ***Example 53: Extract/Cell Supernatant Screening.***

A large number of mammalian receptors exist for which there remains, as yet, no  
20 cognate activating ligand (agonist). Thus, active ligands for these receptors may not be included within the ligands banks as identified to date. Accordingly, the colon cancer antigen of the invention can also be functionally screened (using calcium, cAMP, microphysiometer, oocyte electrophysiology, etc., functional screens) against tissue extracts to identify its natural ligands. Extracts that produce positive functional responses can be sequentially  
25 subfractionated until an activating ligand is isolated identified.

### ***Example 54: Calcium and cAMP Functional Assays.***

Seven transmembrane receptors which are expressed in HEK 293 cells have been  
30 shown to be coupled functionally to activation of PLC and calcium mobilization and/or cAMP stimulation or inhibition. Basal calcium levels in the HEK 293 cells in receptor-transfected or vector control cells were observed to be in the normal, 100 nM to 200 nM,

range. HEK 293 cells expressing recombinant receptors are loaded with fura 2 and in a single day >150 selected ligands or tissue/cell extracts are evaluated for agonist induced calcium mobilization. Similarly, HEK 293 cells expressing recombinant receptors are evaluated for the stimulation or inhibition of cAMP production using standard cAMP quantitation assays. Agonists presenting a calcium transient or cAMP fluctuation are tested in vector control cells to determine if the response is unique to the transfected cells expressing receptor.

*Example 55: ATP-binding assay.*

The following assay may be used to assess ATP-binding activity of the colon or colon cancer related polypeptides of the invention.

ATP-binding activity of the colon or colon cancer related polypeptides of the invention may be detected using the ATP-binding assay described in U.S. Patent 5, 858, 719, which is herein incorporated by reference in its entirety. Briefly, ATP-binding to colon or colon cancer related polypeptides of the invention is measured via photoaffinity labeling with 8-azido-ATP in a competition assay. Reaction mixtures containing 1 mg/ml of the ABC transport protein of the present invention are incubated with varying concentrations of ATP, or the non-hydrolyzable ATP analog adenylyl-5'-imidodiphosphate for 10 minutes at 4°C. A mixture of 8-azido-ATP (Sigma Chem. Corp., St. Louis, MO.) plus 8-azido-ATP (  $-^{32}\text{P}$ -ATP) (5 mCi/ $\mu\text{mol}$ , ICN, Irvine CA.) is added to a final concentration of 100  $\mu\text{M}$  and 0.5 ml aliquots are placed in the wells of a porcelain spot plate on ice. The plate is irradiated using a short wave 254 nm UV lamp at a distance of 2.5 cm from the plate for two one-minute intervals with a one-minute cooling interval in between. The reaction is stopped by addition of dithiothreitol to a final concentration of 2mM. The incubations are subjected to SDS-PAGE electrophoresis, dried, and autoradiographed. Protein bands corresponding to the particular colon or colon cancer related polypeptides of the invention are excised, and the radioactivity quantified. A decrease in radioactivity with increasing ATP or adenylyl-5'-imidodiphosphate provides a measure of ATP affinity to the colon or colon cancer related polypeptides.

*Example 56: Small Molecule**Screening.*

This invention is particularly useful for screening therapeutic compounds by using the colon or colon cancer related polypeptides of the invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a colon or colon cancer related polypeptide of the invention.

Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the colon or colon cancer related polypeptides of the invention. These methods comprise contacting such an agent with a colon or colon cancer related polypeptide of the invention or a fragment thereof and assaying for the presence of a complex between the agent and the colon or colon cancer related polypeptides or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the colon or colon cancer related polypeptides of the invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the colon or colon cancer related polypeptides of the invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is herein incorporated by reference in its entirety. Briefly stated, large numbers of different small molecule test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The test compounds are reacted with colon or colon cancer related polypeptides of the invention and washed. Bound colon or colon cancer related polypeptides are then detected by methods well known in the art. Purified colon or colon cancer related polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding colon or colon cancer related polypeptides of the invention specifically compete with a test compound for binding to the colon or colon cancer related polypeptides or fragments thereof. In this manner, the antibodies are used to  
5 detect the presence of any peptide which shares one or more antigenic epitopes with a colon or colon cancer related polypeptides.

***Example 57: Phosphorylation Assay.***

10 In order to assay for phosphorylation activity of the colon or colon cancer related polypeptides of the invention, a phosphorylation assay as described in U.S. Patent 5,958,405 (which is herein incorporated by reference) is utilized. Briefly, phosphorylation activity may be measured by phosphorylation of a protein substrate using gamma-labeled  $^{32}\text{P}$ -ATP and quantitation of the incorporated radioactivity using a gamma radioisotope counter. The colon  
15 or colon cancer related polypeptides of the invention are incubated with the protein substrate,  $^{32}\text{P}$ -ATP, and a kinase buffer. The  $^{32}\text{P}$  incorporated into the substrate is then separated from free  $^{32}\text{P}$ -ATP by electrophoresis, and the incorporated  $^{32}\text{P}$  is counted and compared to a negative control. Radioactivity counts above the negative control are indicative of phosphorylation activity of the colon or colon cancer related polypeptides of the invention.

20  
***Example 58: Detection of Phosphorylation Activity (Activation) of Colon or Colon Cancer Related Polypeptides of the Invention in the Presence of Colon or Colon Cancer Related Polypeptides Ligands.***

25 Methods known in the art or described herein may be used to determine the phosphorylation activity of the colon or colon cancer related polypeptides of the invention. A preferred method of determining phosphorylation activity is by the use of the tyrosine phosphorylation assay as described in US 5,817,471 (incorporated herein by reference).

30  
***Example 59: Identification Of Signal Transduction Proteins That Interact With Colon or Colon Cancer Related Polypeptides Of The Present Invention.***

The inventive purified colon or colon cancer related polypeptides of the invention are research tools for the identification, characterization and purification of additional signal transduction pathway proteins or receptor proteins. Briefly, labeled receptor PTK polypeptide is useful as a reagent for the purification of molecules with which it interacts. In one embodiment of affinity purification, receptor PTK polypeptide is covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as carcinoma tissues, is passed over the column, and molecules with appropriate affinity bind to the receptor PTK polypeptides, or specific phosphotyrosine-recognition domains thereof. The receptor PTK polypeptide interacting protein-complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate cDNA library.

#### ***Example 60: IL-6 Bioassay.***

To test the proliferative effects of the colon or colon cancer related polypeptides of the invention, the IL-6 Bioassay as described by Marz *et al.* is utilized (*Proc. Natl. Acad. Sci., U.S.A.*, 95:3251-56 (1998), which is herein incorporated by reference). Briefly, IL-6 dependent B9 murine cells are washed three times in IL-6 free medium and plated at a concentration of 5,000 cells per well in 50  $\mu$ l, and 50  $\mu$ l of the IL-6-like polypeptide is added. After 68 hrs. at 37°C, the number of viable cells is measured by adding the tetrazolium salt thiazolyl blue (MTT) and incubating for a further 4 hrs. at 37°C. B9 cells are lysed by SDS and optical density is measured at 570 nm. Controls containing IL-6 (positive) and no cytokine (negative) are utilized. Enhanced proliferation in the test sample(s) relative to the negative control is indicative of proliferative effects mediated by colon or colon cancer related polypeptides of the invention.

#### ***Example 61: Support of Chicken Embryo Neuron Survival.***

To test whether sympathetic neuronal cell viability is supported by the colon or colon cancer related polypeptides of the invention, the chicken embryo neuronal survival assay of Senaldi *et al* is utilized (*Proc. Natl. Acad. Sci., U.S.A.*, 96:11458-63 (1998), which is herein

incorporated by reference). Briefly, motor and sympathetic neurons are isolated from chicken embryos, resuspended in L15 medium (with 10% FCS, glucose, sodium selenite, progesterone, conalbumin, putrescine, and insulin; Life Technologies, Rockville, MD.) and Dulbecco's modified Eagles medium [with 10% FCS, glutamine, penicillin, and 25 mM  
5 Hepes buffer (pH 7.2); Life Technologies, Rockville, MD.], respectively, and incubated at 37°C in 5% CO<sub>2</sub> in the presence of different concentrations of the inventive purified IL-6-like polypeptide, as well as a negative control lacking any cytokine. After 3 days, neuron survival is determined by evaluation of cellular morphology, and through the use of the colorimetric assay of Mosmann (Mossmann, T., *J. Immunol. Methods*, 65:55-63 (1983)). Enhanced  
10 neuronal cell viability as compared to the controls lacking cytokine is indicative of the ability of the inventive purified IL-6-like polypeptide(s) to enhance the survival of neuronal cells.

#### ***Example 62: Assay for Phosphatase Activity.***

15 The following assay may be used to assess serine/threonine phosphatase (PTPase) activity of the colon or colon cancer related polypeptides of the invention.

In order to assay for serine/threonine phosphatase (PTPase) activity, assays can be utilized which are widely known to those skilled in the art. For example, the serine/threonine phosphatase (PSPase) activity is measured using a PSPase assay kit from New England  
20 Biolabs, Inc. Myelin basic protein (MyBP), a substrate for PSPase, is phosphorylated on serine and threonine residues with cAMP-dependent Protein Kinase in the presence of [ $\gamma$ -<sup>32</sup>P]ATP. Protein serine/threonine phosphatase activity is then determined by measuring the release of inorganic phosphate from <sup>32</sup>P-labeled MyBP.

#### ***Example 63: Interaction of Serine/Threonine Phosphatases with other Proteins.***

The colon or colon cancer related polypeptides of the invention with serine/threonine phosphatase activity as determined in Example 62 are research tools for the identification,  
30 characterization and purification of additional interacting proteins or receptor proteins, or other signal transduction pathway proteins. Briefly, a labeled colon or colon cancer related polypeptides of the invention is useful as a reagent for the purification of molecules with



which it interacts. In one embodiment of affinity purification, colon or colon cancer related polypeptides of the invention is covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as neural or liver cells, is passed over the column, and molecules with appropriate affinity bind to the colon or colon cancer related polypeptides of the invention. The colon or colon cancer related polypeptides of the invention-complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate cDNA library.

#### ***Example 64: Assaying for Heparanase Activity.***

In order to assay for heparanase activity of the colon or colon cancer related polypeptides of the invention, the heparanase assay described by Vlodavsky et al is utilized (Vlodavsky, I., et al., Nat. Med., 5:793-802 (1999)). Briefly, cell lysates, conditioned media or intact cells ( $1 \times 10^6$  cells per 35-mm dish) are incubated for 18 hrs at 37°C, pH 6.2-6.6, with  $^{35}\text{S}$ -labeled ECM or soluble ECM derived peak I proteoglycans. The incubation medium is centrifuged and the supernatant is analyzed by gel filtration on a Sepharose CL-6B column (0.9 x 30 cm). Fractions are eluted with PBS and their radioactivity is measured. Degradation fragments of heparan sulfate side chains are eluted from Sepharose 6B at  $0.5 < K_{av} < 0.8$  (peak II). Each experiment is done at least three times. Degradation fragments corresponding to "peak II," as described by Vlodavsky et al., is indicative of the activity of the colon or colon cancer related polypeptides of the invention in cleaving heparan sulfate.

#### ***Example 65: Immobilization of biomolecules.***

This method provides a method for the stabilization of colon or colon cancer related polypeptides of the invention in non-host cell lipid bilayer constructs (see, e.g., Bieri et al., Nature Biotech 17:1105-1108 (1999), hereby incorporated by reference in its entirety herein) which can be adapted for the study of colon or colon cancer related polypeptides of the invention in the various functional assays described above. Briefly, carbohydrate-specific chemistry for biotinylation is used to confine a biotin tag to the extracellular domain of the

colon or colon cancer related polypeptides of the invention, thus allowing uniform orientation upon immobilization. A 50uM solution of colon or colon cancer related polypeptides of the invention in washed membranes is incubated with 20 mM NaIO<sub>4</sub> and 1.5 mg/ml (4mM) BACH or 2 mg/ml (7.5mM) biotin-hydrazide for 1 hr at room temperature (reaction volume, 150ul). Then the sample is dialyzed (Pierce Slidealizer Cassett, 10 kDa cutoff; Pierce Chemical Co., Rockford IL) at 4C first for 5 h, exchanging the buffer after each hour, and finally for 12 h against 500 ml buffer R (0.15 M NaCl, 1 mM MgCl<sub>2</sub>, 10 mM sodium phosphate, pH7). Just before addition into a cuvette, the sample is diluted 1:5 in buffer ROG50 (Buffer R supplemented with 50 mM octylglucoside).

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties. Moreover, the hard copy of and the corresponding computer readable form of the Sequence Listing of U.S. Patent Application Serial No. 60/157,137 and 60/163,280 are also incorporated herein by reference in its entirety.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209059
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States) Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable) The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<b>For receiving Office use only</b> <input type="checkbox"/> This sheet was received with the international application Authorized officer	<b>For International Bureau use only</b> <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
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**ATCC Deposit No. 209059****Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209059

Page 3

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>20 May 1997</u>	Accession Number <u>209060</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g. "Accession Number of Deposit")          	

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ATCC Deposit No. 209060

Page 2

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209060

Page 3

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.



Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u> .	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209061
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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**ATCC Deposit No. 209061****Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209061

Page 3

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>20 May 1997</u>	Accession Number <u>209062</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<u>Europe</u> In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")          	
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**ATCC Deposit No. 209062****Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209062

Page 3

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

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**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209063
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
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**ATCC Deposit No. 209063****Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.



**ATCC Deposit No. 209063****Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

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**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

2173

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209064
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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**ATCC Deposit No. 209064****Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209064

Page 3

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

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**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>20 May 1997</u>	Accession Number <u>209065</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")          	

<b>For receiving Office use only</b>	<b>For International Bureau use only</b>
<input type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer	Authorized officer

**ATCC Deposit No. 209065****Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

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ATCC Deposit No. 209065

Page 3

**DENMARK**

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Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

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Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>20 May 1997</u>	Accession Number <u>209066</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<u>Europe</u> In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
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**ATCC Deposit No. 209066****Page 2****CANADA**

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**NORWAY**

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**FINLAND**

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**UNITED KINGDOM**

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ATCC Deposit No. 209066

Page 3

**DENMARK**

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**NETHERLANDS**

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Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209067
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	
For receiving Office use only <input type="checkbox"/> This sheet was received with the international application Authorized officer	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer

**ATCC Deposit No. 209067****Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

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**FINLAND**

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**UNITED KINGDOM**

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ATCC Deposit No. 209067

Page 3

**DENMARK**

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**SWEDEN**

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**NETHERLANDS**

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Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209068
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States) Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
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<b>For receiving Office use only</b> <input type="checkbox"/> This sheet was received with the international application Authorized officer	<b>For International Bureau use only</b> <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
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**ATCC Deposit No. 209068****Page 2****CANADA**

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**NORWAY**

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**AUSTRALIA**

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**FINLAND**

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**UNITED KINGDOM**

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**ATCC Deposit No. 209068****Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

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**NETHERLANDS**

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Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

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<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209069
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
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ATCC Deposit No. 209069

Page 2

**CANADA**

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ATCC Deposit No. 209069

Page 3

**DENMARK**

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Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 12 January 1998	Accession Number 209579
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<b>For receiving Office use only</b> <input type="checkbox"/> This sheet was received with the international application  Authorized officer	<b>For International Bureau use only</b> <input type="checkbox"/> This sheet was received by the International Bureau on:  Authorized officer
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**ATCC Deposit No. 209579****Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**ATCC Deposit No. 209579****Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u> .	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>12 January 1998</u>	Accession Number <u>209578</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<u>Europe</u> In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). <u>Continued on the Attached Pages 2 &amp; 3</u>	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")          	
<b>For receiving Office use only</b> <input type="checkbox"/> This sheet was received with the international application  Authorized officer	<b>For International Bureau use only</b> <input type="checkbox"/> This sheet was received by the International Bureau on:  Authorized officer

**ATCC Deposit No. 209578****Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.



**ATCC Deposit No. 209578****Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 16 July 1998	Accession Number 203067
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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Authorized officer	Authorized officer

**ATCC Deposit No. 203067****Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 203067

Page 3

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 16 July 1998	Accession Number 203068
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States) Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable) The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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**ATCC Deposit No. 203068**  
**Page 2**

### **CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

### **NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

### **AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

### **FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

### **UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 203068

Page 3

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 01 February 1999	Accession Number 203609
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States) Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable) The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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**ATCC Deposit No. 203609****Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 203609

Page 3

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

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**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 01 February 1999	Accession Number 203610
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	
<b>For receiving Office use only</b> <input type="checkbox"/> This sheet was received with the international application Authorized officer	<b>For International Bureau use only</b> <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer

**ATCC Deposit No. 203610****Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**ATCC Deposit No. 203610****Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 17 November 1998	Accession Number 203485
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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Authorized officer

**ATCC Deposit No. 203485****Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 203485

Page 3

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.



2212

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>18 June 1999</u>	Accession Number <u>PTA-252</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<u>Europe</u> In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")          	

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**ATCC Deposit No. PTA-252****Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**ATCC Deposit No. PTA-252****Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 18 June 1999	Accession Number PTA-253
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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<input type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer	Authorized officer

**ATCC Deposit No. PTA-253****Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**ATCC Deposit No. PTA-253****Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 28 October 1999	Accession Number PTA-881
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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**ATCC Deposit No. PTA-881****Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.



ATCC Deposit No. PTA-881

Page 3

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

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**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>311</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT <span style="float: right;">Further deposits are identified on an additional sheet <input type="checkbox"/></span>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 28 October 1999	Accession Number PTA-882
C. ADDITIONAL INDICATIONS (leave blank if not applicable) <span style="float: right;">This information is continued on an additional sheet <input type="checkbox"/></span>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC). Continued on the Attached Pages 2 & 3	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<div>For receiving Office use only</div> <div><input type="checkbox"/> This sheet was received with the international application</div> <div>Authorized officer</div>	<div>For International Bureau use only</div> <div><input type="checkbox"/> This sheet was received by the International Bureau on:</div> <div>Authorized officer</div>
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**ATCC Deposit No. PTA-882****Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

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**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

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**Page 3**

## **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

## **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

## **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

*What Is Claimed Is:*

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X which is hybridizable to SEQ ID NO:X;

(b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y which is hybridizable to SEQ ID NO:X;

(c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y which is hybridizable to SEQ ID NO:X;

(d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y which is hybridizable to SEQ ID NO:X;

(e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y which is hybridizable to SEQ ID NO:X, having biological activity;

(f) a polynucleotide which is a variant of SEQ ID NO:X;

(g) a polynucleotide which is an allelic variant of SEQ ID NO:X;

(h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;

(i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a protein.

3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y, which is hybridizable to SEQ ID NO:X.

4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X, which is hybridizable to SEQ ID NO:X.

5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.

11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

- (a) a polypeptide fragment of SEQ ID NO:Y;
- (b) a polypeptide fragment of SEQ ID NO:Y, having biological activity;
- (c) a polypeptide domain of SEQ ID NO:Y;
- (d) a polypeptide epitope of SEQ ID NO:Y;
- (e) a full length protein of SEQ ID NO:Y;
- (f) a variant of SEQ ID NO:Y;
- (g) an allelic variant of SEQ ID NO:Y; or
- (h) a species homologue of the SEQ ID NO:Y.

12. The isolated polypeptide of claim 11, wherein the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

15. A method of making an isolated polypeptide comprising:  
(a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and  
(b) recovering said polypeptide.

16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

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(a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

(a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

22. A method of identifying an activity in a biological assay, wherein the method comprises:

(a) expressing SEQ ID NO:X in a cell;

(b) isolating the supernatant;

(c) detecting an activity in a biological assay; and

(d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 20.



## SEQUENCE LISTING

<110> Birse et. al.

<120> Colon and Colon Cancer Associated Polynucleotides and Polypeptides

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<140> Unassigned

<141> September 28, 2000

<150> 60/157,137

<151> September 29, 1999

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<151> November 3, 1999

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6

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agaaaagggtg gcatggaagt tcgcaatctt tgtattcttg gggaaaagtct gattacactg 780
cacagtccag gttgtgtgac actagaactc attataaatc aacttcaagg tgaaaaattg 840
gaaacattta ccccgaggga tattgtggcc ctttatagaa tcttgaggc atgtactgaa 900
aaagtggatg aacaccaaac atttttaaat aagataaaca actttnccct atcaatagtt 960
tccaacctga gtcctaaatt gattagncaa atgctcactg ccctgggtgg tcttgatcaa 1020
agtcaagcat ttcctctgat tataaaaatt ggcaaaaatg gtcgtgaggc atgtcccaca 1080
tttcacttaa cgaggagctt aggagagtct tttgaggcgt 1120
```

<210> 13

<211> 600

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (50)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (571)



<223> n equals a,t,g, or c

<400> 13

```
ctagatcgtc agggaggaag ggtcagttgg gtgcctgttt ttctgttttn agtcctttaa 60
aatgagtaga agcaacctgt taccctggaa agagcactgg acatagacct agtgctgcgt 120
gatgttgagc acgtttcttc ttccctttga gtcccagttt cccttttggt tacaggggga 180
tagtagcccc cagggatcat gtgaaagtga gaaagccctt ttcacactgt ggagcgggtc 240
agatgtggga aacctcaaag atggttgccc attttaaatac ctttcatctc tcatctctct 300
ttcttctctc ctttctgccc tgacgtagcc atggttgggt gggtagaggcc agaagaaact 360
gcctccgmaa gaggtagcag ccgctcaggt ggctctgctg gcatcggagc ccacagaagt 420
gaggagtggc cgatggamct gccctccaaa tgtgcctgac tctgggtctt gctgtcactg 480
ggatttcctg ggcattggcag acagaaagaa agatagtttg accaagtcgt aggaagcttg 540
attccagcgg gtaaaaaagg gggcagggaa ntgcgtccctt ttattttttg ctttcaggag 600
```

<210> 14

<211> 807

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (773)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (786)

<223> n equals a,t,g, or c

<400> 14

```
caattaagggt tgtacaaatt ataataatgc atctctatct tcatactttg aatggcaaac 60
gctattttatg cataaatatt ttcatTTTTaa gtaatatatg aagtgtaaat actcgatata 120
taagtataga ttttaaagat atgggacttt attttcacat aagtcaatag atgtttctct 180
agaacaaaat atttagtaaa gctttataaa ttatatataa aggaagcggg gaacatgtat 240
tttttaacat agaacagaag tgacttcatt ctttttagac atcagaaatg ttaaagttga 300
ttcccaatat ttgttgtact tttttgtagc aaatgttaaa aatcacgagt taccatgtat 360
agaatgtgga ctgtcatgtt gatatcattg tacagtata agccattttw atctgtatac 420
atttcaccaa tttattaaca ggttgaatat ttgtttcttt ttagaacatt ttatttatac 480
tgtgaagact ttgttatacc ttatttgcta caacatagat catatcattg ctactttgac 540
ttagcatttg catcataaac ataattatga tgtttttttc atgtccctc caggggctca 600
gtcacttgaa gaaactgttg ctaaccaagc tcttgactct gtttccctta atgatacaag 660
tctctgtacc agcgctttat gttaattacc aaaactctcc tgcattcagag catgatattc 720
ataataggag atactgsaat aaaatgrttw ggctgtaaaa atttggaggc acnaattttc 780
caattncaat ggcaaattgg catgggtg 807
```

<210> 15

<211> 416

<212> DNA

<213> Homo sapiens

<220>

10

<221> misc feature  
 <222> (1)  
 <223> n equals a,t,g, or c

<400> 15  
 ngttttggga ttattataag ttcttgtgtc ttaaggccat ctgcttttat atccagtgat 60  
 gtgggatttt aatcagccat taattaggta agcattcact ttgaggacaa tattctgttt 120  
 tatcttgggt agcatggaca gtttgtcaca gaaataagtt ccctattcaa acttggaatt 180  
 agctgattca gagtaacata ttaataatat aaaaatggcc ataccctttt atggcgtaac 240  
 attatttcta ggtattgttt ctaaggaaat aattttaaat attgggaaaa aatattttta 300  
 caatttacag tctgtctgac atttggtaaa tagctaattg tgatatattc atattaggag 360  
 atagggtgca gccactaaaa tgattttgaa gtattgtcca ttagtaatgg taattt 416

<210> 16  
 <211> 752  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (40)  
 <223> n equals a,t,g, or c

<400> 16  
 ggcctgggct ccttccgaat ggtggcgcct ctgagccagn ttctgaggag gagtcggagg 60  
 aggagcctga atgtttggag atagacttca agtcccggac cttatccgtg cgccgcttcg 120  
 gtttgcaggt gacctttgcg tgcgggcgcc cttcttgatt gacctgatg agctgtagct 180  
 ctgatggccc ctccctcggg aatgattagg gtgacggctg kccggggctc gttcgagtgg 240  
 cgcccggccg gtggtgaccc gaacaggaga gcgggacggc gaccattctc tcgggagggg 300  
 cccatytgga gaaagtcctc tcgcttggtc aaactaggag ggcgatagca ccggccttac 360  
 tgcgacgatg acaaagtaca acacaccgtc tggcgcgaa gagatgctcg agaacccttt 420  
 gctgttggtt ttttctcgt gtccctcgaa accaagggaa atgcggctct gtgggttctg 480  
 ttaacgtcag catttaataa gtgaactcta aatgcattgc cccttatggg tgcgctggcc 540  
 tcctgagttg actcagctct tgcaacgtag ctagttagata accctcgaaa tatagcgaat 600  
 tgagatgtgc tatattgtaa aatacgggac ttagtacgaa aaaactgatg taaaaattat 660  
 ctcaatactt ttaataactg attacatgtt ggaatataat gttttgcata tattgggtca 720  
 aataaaaatg ttattaattt caaaaaaaaa aa 752

<210> 17  
 <211> 481  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (442)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (447)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (448)

<223> n equals a,t,g, or c

<400> 17

```
ggcaccgagtt tcaaaccaac actgaaattc tgtggcatca catatattgg gccttgatgt 60
catgacagak caaaatcatt tgatatccct ttctccattc taggtttttc tttttttcag 120
taactgattt accttgatca cttttcaact tccatattct tcatatagta aaaggcaaag 180
tgttgaagat actacgggtg ggtagtagtt gaaaattatt gccgtcatta ttacatact 240
taagacatat tagcaagttg atccaaaatg ggaggcctta tagatgtgct tgggggaaaa 300
tgaaggggag aaagtagcca tacaggagtt caaagaattc catgcccttc agattagccc 360
attaccagaa acatcatgaa agtattttta aaactaatta ttactacag tgtatttcac 420
ttgtcttggt tgtctgaaca cnagganngc taaattagca agttttttta ggaggtattt 480
t 481
```

<210> 18

<211> 912

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (875)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (881)

<223> n equals a,t,g, or c

<400> 18

```
aattcggcac aggatcagac ttccctttcaa ctgtcctccc ctccaagcag accacctgtc 60
cccttctatc ccagctcaga gcagctgacc caactcagaa tctctttcct acaggatgaa 120
gtgccttttg aatgttattt taagccgaga gttaattttt ctacacaaca tatttccaga 180
catcttttag tcttttattg tcttagatac tataagaaga tgaacatgac aattttctag 240
aacctggtag cgtgtgtgtg tgtggcgggg ggtgctgagg gaggggagtg agtcacagga 300
gcctgtcccc caacagggtg gactgctctg acaacctgtg gcatgctgca gggtcaggct 360
cctgatagga ggatttcatg actatgtcat tgtctccact catttttgac ccagtttga 420
atgtatctgc aattgtgtgg ctcaacactt taggaaacaa tagattattt tatattatta 480
tttctgatgg tgacaagttt gtcttgaggt cacattttct ccttgaaaag tgacatcctg 540
tcaacttctg tctcacacta ctgccataca tttgtgtttt ttgttggtat tgtttgggta 600
gagcagttac aagaaacctt aaaaccttg gatataaaag aaatctgttt attgattttt 660
aaatctttcc tttccaaaag ctgggataca catgggagct gtttggggaa ttttcttgc 720
tgctaccgag ctgccaccaa atgggaattg accaggcggg ctgtttacac tgtttctttg 780
gccactgtgg ccyatggctc aggaatatgg ctcaactggc aaggcttacc aaactcgggg 840
acaggggggtc agggaaacag gaggggtgtt cccntcccc nttggcaggc cttcccaccc 900
acctggttaa cc 912
```

12

<210> 19  
 <211> 507  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (489)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (492)  
 <223> n equals a,t,g, or c

<400> 19  
 ggatacatag gaagttgacc tcgggggtatc atggagagtg tccctcctag tggctggagg 60  
 tagggacagt tggttgtggg gctggagaga ggttgtgggg aggaagcgag gatgcgtgcc 120  
 tgccactagg atctgcatcc ccgagcccaa gccaggaggg atttccctta ggcaacacca 180  
 tcccagggag atctgccaca atttgcgttt cacagctraa gacgccgagg cttagagagc 240  
 tcgacctcct caaggtcaca ccaactgggta aatagaggga tgcagactca ggtttttgcta 300  
 tgtgctcaca tttcaacttt atgcttaaca tgaatggaaa aatatgaaag taaatagtga 360  
 aaaggtgagt tatgagctta gattacctag attattccag tatcccatgg aagctgagga 420  
 cttattccgc tttccacacc gaacactaaa tgtggaccag tatcaagaac cctcctgtcc 480  
 ccacgcagnt anaaccaggt ggcttct 507

<210> 20  
 <211> 410  
 <212> DNA  
 <213> Homo sapiens

<400> 20  
 ggcagagcca aaagagggtt cttggatctc acgcaacaaa gagttcgggg cgagtccata 60  
 gagtaaagtg aaagcaagtt catcaagaaa gcaaaggaat aaagaatgcc tactccatag 120  
 gcagagcagt ggctttggct gctcagctgc ttgtacttgt tacttcttga gtatatgcta 180  
 aacaagggat tgattactcc ttgttttagca gttttctggg aaaggagtgg gcaattccca 240  
 gaactgaggg ttcttccct ttttaagacc atattagggt gacttcttga tgttgccatg 300  
 gcatttgtaa actgtcatgg cgctrtgggw gtgtctttta gcatgctaat gctttataat 360  
 tagcgtataa tgagcagtga ggacaaccag aggtcactct tgtctgtgcc 410

<210> 21  
 <211> 496  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (36)  
 <223> n equals a,t,g, or c

<220>

## 13

<221> misc feature  
 <222> (356)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (443)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (454)  
 <223> n equals a,t,g, or c

<400> 21  
 ggcacgaggg cacs mkcaaa ccttggtctt cctctnctgt tgcattcctt ccctaccctt 60  
 ccctcccagg tgctcggtac tttaccwagt ttctatatat cagtgtttta tgttggaatt 120  
 tttccttggt tttattttac tagttggtaa accctgttta tgctgaaaca aataaggaaa 180  
 tggatatatt gaccatatgt gttattcata gaagacagta tgatcaaatt tgccaaaaac 240  
 aagcaaacaa aacttaattc ctgrgaagta tgccttattt ttattgatct gctttgtctt 300  
 acaattaagg tccaagagct tgggttaaact gtattatttg cctaagtata aaaganaact 360  
 tgaactgcat tgcaatattg acgttcttta aaatgagaga cactgtcaag taatttaatc 420  
 cagagatcag ccaccagatt tagnaatgcct atgnatgtgt gtgtgttggg agtgggtttt 480  
 tcctttaaac caccca 496

<210> 22  
 <211> 363  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (313)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (333)  
 <223> n equals a,t,g, or c

<400> 22  
 ggcacgagta taaatgatgg tgtggatgtc aggggtgaggg aggagacaaa accacgatga 60  
 ccctagctt tgtggcctga actgtgggtg gctgagggga tcgttaattg aatggggcag 120  
 actgaggtt gtraggaaga tcagagtctg gttcttgaca tgagatgcc ttcaaactc 180  
 tcttcaactca ggtgcaacta gggatacaga aacactgkat atttcaacag cagaaattga 240  
 atggggggat tgatagcsct ggcgagggaa gcagctggta aagaagacag atggcaccct 300  
 gagacagccc agnggtggaa taggaccccc agngtgcagg gattaaagtt ccatgggttg 360  
 gtg 363

<210> 23  
 <211> 239

14

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (238)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 23

```
ctcaggctgc tgcacgtggs catccgcate cggccttityt tgcacagttt gaccgtggag 60
agcgcggacc tgcagggctg ctgctttgct gggcctggca gccccaccc gagaagatgg 120
agttccggac ggcattctatc cgcctctttg ggcacttaac aaggctctgcc acggagactg 180
taaggacgtc ttcttggacc aagtgggtggg cgggctggcg ccttgcctgct gcacctgna 239
```

&lt;210&gt; 24

&lt;211&gt; 461

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (426)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (428)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 24

```
aacaattaag tctttaggaa tgtgtaacca gaactatggt agtattgctt ataaaaacttt 60
agttagggttc aatatataca tatatacatc tctatatagg tatatagatt tgcattttgt 120
cttgtaaaat tttatttgaa taaattcttc ctgtaggtaa tgggaaacaa aattaatagt 180
tcatatgtca tctatagcat ttctatattt gaaagtagcc caatataaaa cttttgattc 240
taaaattaaa ccagcagcct attacaagca cattctttga ttgagtcatt gggtataaac 300
ttactaaatg cagrgaagc agccaattta gggaaacttc tgagttggtg gggacactgt 360
tggattaata atgtacggtg tgaattaagt gatgccttaa cttggatttt acattttaag 420
gttaangngg gggcatatgg tcagccaact tagggggcat t 461
```

&lt;210&gt; 25

&lt;211&gt; 453

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (442)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 25

```
accagaccaa ccctatgaat ggctttcata taaacagggt gcagaattgt cggagtgcac 60
```

## 15

```

aggctcagca ctgatccaga agggcttcaa gactgccccca gatcagttca ttggcatctt 120
tgctcaaaat agacctgagt ggggtgattat tgaacaagga tgctttgctt attcgatggg 180
gatcgttcca ctttatgata cccttggaata tgaagccatc acgtacatag tcaacaaagc 240
tgaactctct ctgggtttttg ttgacaagcc agagaaggcc aaactcttat tagagggtgt 300
agaaaataag ttaataaccag gccttaaaat catagtgtgc atggatgcct acggmagtaa 360
ctggtggaac gaggccagag gtgtgggggtg gaagtcacca gcatgaaggc gatggaggac 420
ctgggaagag ccaacagacg gnagcccaag cct 453

```

&lt;210&gt; 26

&lt;211&gt; 1940

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (576)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 26

```

ggcagaggtc ctacagtgcag ggcaacagga ctttaggttc aagatgggtga ctgcagccat 60
gctgctacag tgctgcccag tgcttgcccg gggccccaca agcctcctag gcaagggtgg 120
taagactcac cagttcctgt ttggtattgg acgctgtccc atcctggcta cccaaggacc 180
aaactgttct caaatccacc ttaaggcaac aaaggctgga ggagattctc catcttgggc 240
gaagggccac tgtcccttca tgctgtcgga actccaggat ggggaagagca agatttgtga 300
gaaggcagcc ccagaagtcc aggaagatgt gaaggctttc aagacagatc tgcctagctc 360
cctggtctca gtcagcctaa ggaagccatt ttccgggtccc caggagcagg agcagatctc 420
tgggaaggtc acacacctga ttcagaacaa tatgcctgga aactatgtct tcagttatga 480
ccagtttttc agggacaaga tcatggagaa gaaacaggat cacacctacc gtgtgttcaa 540
gactgtgaac cgctgggctg atgcatatcc ctttgnccca acatttctct gaggcattctg 600
tggcctcaaa ggatgtgtcc gtctggtgta gtaatgatta cctggggcat gagccgacac 660
cctcaggctc tgcaagccac acaggagacc ctgcagcgtc atgggtgctgg agctgggtggc 720
acccgcaaca tctcaggcac cagtaagttt catgtggagc ttgagcagga gctggctgag 780
ctgcaccaga aggactcagc cctgctcttc tctcctgct ttgttgccaa tgactctact 840
ctcttcacct tggccaagat cctgccaggg tgcgagattt actcagacgc aggcaaccat 900
gcttccatga tccaaggat ccgtaacagt ggagcagcca agtttgtctt caggcacaat 960
gaccctgacc acctaaagaa acttctagag aagtctaacc ctaagatacc caaaattgtg 1020
gcctttgaga ctgtccactc catggatggg gccatctgtc ccctcgagga gttgtgtgat 1080
gtgtccacc agtatggggc cctgaccttc gtggatgagg tccatgctgt aggactgtat 1140
gggtcccggg gcgctgggat tggggagcgt gatggaatta tgcataagat tgacatcatc 1200
tctggaactc ttggcaaggc ctttggctgt gtgggcggt acattgccag caccctgac 1260
ttggtggaca tgggtgcgctc ctatgctgca ggcttcatct ttaccacttc tctgcccccc 1320
atggtgctct ctggagctct agaactctgt cggctgctca agggagagga gggccaagcc 1380
ctgaggcgag cccaccagcg caatgtcaag cacatgcgcc actactcatg gacagggggc 1440
ttcctgtcat cccctgcccc agccacatca tccccatccg ggtgggcaat gcagcactca 1500
acagcaagct ctgtgatctc ctgctctcca agcatggcat ctatgtgcag gccatcaact 1560
acccaactgt ccccgggggg gaagagctcc tgcgcttggm accctcccc caccacagcc 1620
ctcagatgat ggaagatttt gtggagaagc tgctgctggc ttggactgcg gtggggctgc 1680
ccctccagga tgtgtctgtg gctgcctgca atttctgtcg ccgtcctgta cactttgagc 1740
tcatgagtga gtgggaacgt tctacttcg ggaacatggg gccccagtat gtcaccacct 1800
atgcctgaga agccagctgc ctaggattca caccacact gcgcttcaact tgggtccagg 1860
cctactcctg tcttctgtct tgttgtgtgc ctctagctga attgagccta aaaataaagc 1920

```

acaaaccaca gcaaaaaaaaaa

1940

<210> 27  
 <211> 864  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (552)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (773)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (856)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (863)  
 <223> n equals a,t,g, or c

<400> 27  
 tctaaatcca ttacaaatct gcttagcttc taaatatattc atcaatgagg aaatcccagc 60  
 cctacaactt cggaacagtg aaatattagt ccagggatcc agtgagagac acagaagtgc 120  
 tagaagccag tgctcgtgaa ctaaggagaa aaagaacaga caagggaaca gcctggacat 180  
 ggcatacagag atccacatga caggcccaat gtgcctcatt gagaacacta atgggcgact 240  
 gatggcgaat ccagaagctc tgaagatcct ttctgccatt acacagccta tgggtggtggt 300  
 ggcaattgtg ggcctctacc gcacaggcaa atcctacctg atgaacaagc tggctggaaa 360  
 gaaaaagggc ttctctcttg gctccacggg gcagtctcac actaaaggar tctggatgtg 420  
 gtgtgtgccc caccccaaga agccaggcca catcctagtt ctgctggaca ccgaggggtc 480  
 gggagatgta gagaagggtg acaaccagaa tgactcctgg atcttcgccc tggccgtcct 540  
 cctgarcagc ancttctrtgt acaatagcat aggaaccatt aaccagcagg ccatggacca 600  
 actgcactat caatctcggg cctgaacctc acctccaaaa agaaagcgac ttcagtagaa 660  
 agtgggggtca gaaggaagag tgtggtcctg gccagctag acaaaaagcg ggatgacttt 720  
 tgtaaacaga atcaggaagc atcatcagat cgttgctcag ctttacttca ggnccatttt 780  
 agtcctctag aagaagaagt gaaggcgagg gaattttatt tcgaaaacca aggggggtaa 840  
 ccgtctctgt tattcnagaa agnt 864

<210> 28  
 <211> 703  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature



17

&lt;222&gt; (549)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (612)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 28

```

gggtcgaccc acgcgtccgc caggagtagg tcctatcagt gcccccccag agtagagagc 60
aataagagcc cagcccagtg cagtcccggc tgtgttttcc tacctggtga tcagaagtgt 120
ctggtttgct tggctgcccc tttgcctctt gagtgggcag ccctgggctt gggccctcc 180
ctccggccct cagtgttggc tctgcagaag ctctgggggt cccttcaagt gcacgagggg 240
ttaggtctgt gtccctgagt cctccattct gtactggggg gctggctagg acctggggct 300
gtggcctctc aggggggcag ctctccatgg caggcatccc tgccttgggc tgccctcccc 360
cagacccctg accacccctt gggtcctgtc ccccaccaga gcccagctc ctgtctgtgg 420
gggagccatc acggtgttcg tgcagtccat agcgcttctc aatgtgtgtc acccggaacc 480
tgaggagggg ggggaacctg gggtttagga ccacaactca gaggtgctt ggccctcccc 540
tctgaccang cttatcctga gtttggtggc tacttccctc tggcctaagg taggggaggc 600
cttctcagat tntgggggca cattgtgtag cctgacttct gcaggagctc ccaattccag 660
gaaggaaaag agccaaggcc ccacttttgg ggatcagggt ggg 703

```

&lt;210&gt; 29

&lt;211&gt; 337

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (71)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (331)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (332)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 29

```

aggtgacact atagaaggta cgcctgcagg taccggatcc ggaattcccg ggtcgaccca 60
cgcgtccgca nttacattta tgttttagt tctaagtaag accctgagag attttcaaaa 120
aggaattaat gattattttt gtcttccccca ggattggaac gagttactat gctgtttctg 180
ggattgcata atgttcgtca gacctccatg ttccctcgtg atcccaaacg actcactcct 240
taaattcaca ctttgccact taactccagt gtggatgaca gagcgagacc ctgcctcaaa 300
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa nncccc 337

```

&lt;210&gt; 30

## 18

<211> 631  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (524)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (608)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (615)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (630)  
 <223> n equals a,t,g, or c

<400> 30  
 agggaaactca ctgtgggtttt ratttgtatt tycttttttta agtgaaagca rgkttatttaa 60  
 gaaagcaaag gaataaagaa tggctattcc ataggcagag cccattgcca ctcagctgct 120  
 tatacttatt gttacttctt gattgtatgc taaacaaggg gtggattatt catgagtttt 180  
 atgggaaagg ggtgggcagt atctggaact gagggtttct cccctttgta gaccatacag 240  
 ggcaacttcc tgacgttgcc atggtatctg gaaactgtca tgggtgctggt ggaagtgtct 300  
 tttagcatgc tgatgcatta taattagagt ataatgaata gtaaggacaa ccagagggtca 360  
 ctttcacgc catcttggtt ttggtcagct tctttactgc agcctgtttc atcattaagg 420  
 tctttattac ctgtatcttg tgccgacctc ctgtctcatc ctgtgactta gaatgcctaa 480  
 cctcctggga atgtagccca gtgggtctca gccttatttt actncacccc ctaattcaag 540  
 atgggagttt ctctgggttt cagacaaccc ctggacatgt tttccccctt ccctttttac 600  
 agcagaancc ttaantccca acagtcgtan a 631

<210> 31  
 <211> 571  
 <212> DNA  
 <213> Homo sapiens

<400> 31  
 gaattcggca cgagtcaccac cagcccccca aaaaacctct cagtagtttc tttcagtgta 60  
 caaatgatg agcatttttc tatgatgagg ttttaacctat tattcagggt ggtcttttgt 120  
 ttttaaactt ttttttaact aataagattt acggtgtgta ttttatacag aaatgcatta 180  
 taaatgtttt taattgtgtt ctgttttttg cagtctttta gtgccatgcc aattgttctt 240  
 atattctata gaagttcgct caaaatactc aacaggggaa taggcagcgg acagtcagaa 300  
 tggttggaat tttggctttc taagaaaaac tttattttgc ataagcatgt ggtcagatca 360  
 ttttgtgcat atgcagcctg gattggatgt taagtaaata cttgttcagt gccggtacat 420  
 ttacttaaat ctgtttttat ttttgtcatg tagaatacta ctgtgggtcat cataatgtaa 480

## 19

tctattttctg tacctttttt tttttttttt acttttgaagt cttaaataaa atgtataata 540  
 cccaaaaaaa aaaaaaaaaa aaaaaaaaaa a 571

<210> 32  
 <211> 424  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (413)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (414)  
 <223> n equals a,t,g, or c

<400> 32  
 tttctaaaaa tcaggaaaat tagttactaa aaattgctga tcatttttgt ttcattattt 60  
 ttgttatttc aaatgtataa gctctgggat tcttttttga gcaataccta caaagtcagg 120  
 caccagaatg tgcctcagag ctgtgacatt tcaacatgat ggtttttggt tggtttggtt 180  
 ttgtgtcctt tttatttgca gtttttttctg ttgcaacaga aagtggcttg gaagtcttag 240  
 gtgggtatgta acaaattcct tttaaaaatt ttaaagcagt atttaagtat tcttaaattg 300  
 gtaaattcat ttaatgtttt acttctaatt tcttgatctt tggctgtctg gttttattgc 360  
 atttttaaaa aaactgaacc attaagkaat tggaaatgaa tgaagggtgaa atnnctgaac 420  
 ctga 424

<210> 33  
 <211> 1626  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (525)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (542)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (562)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (607)

<223> n equals a,t,g, or c

<400> 33

```

ccacgcgtcc gacgcggcgc acgcggcagc cctgatggcc cggcatgggt taccgctgct 60
gcccctgctg tcgctcctgg tcggcgcgctg gctcaagcta ggaaatggac aggctactag 120
catgggtccaa ctgcaggggtg ggagattcct gatgggaaca aattctccag acagcagaga 180
tggtgaaggg cctgtgcggg aggcgacagt gaaacccttt gccatcgaca tatttcctgt 240
caccaacaaa gatttcaggg attttgtcag ggagaaaaag tatcggacag aagctgagat 300
gtttggatgg agctttgtct ttgaggactt tgtctctgat gagctgagaa acaaagccac 360
ccagccaatg aagtctgtac tctgggtggt tccagtggaa aaggcatttt ggaggcagcc 420
tgcaggtcct ggctctggca tccgagagag actggagcac ccagtgttac acgtgagctg 480
gratgacgcc cgtgcctaata gtgcytkgsg ggggraaacg actgnccac sggagggaag 540
antggggagt ttttcgccc gnaggggggc ttgaarggtc caagtttacc ccattggggg 600
aactggnttc cagccaaacc gcaccaacct gtggcagggg aagttcccca agggagacaa 660
agctgaggat ggcttccatg gagtctcccc agtgaatgct tccccgccc agaacaacta 720
cgggctctat gacctcctgg ggaacgtgtg ggagtggaca gcatcaccgt accaggctgc 780
tgagcaggac atgcgcgtcc tccggggggc atcctggatc gacacagctg atggctctgc 840
caatcaccgg gcccggttca ccaccaggat gggcaacact ccagattcag cctcagacaa 900
cctcggtttc cgctgtgctg cagacgcagg ccggccgcca ggggagctgt aagcagccgg 960
gtggtgacaa ggagaaaagc cttctagggt cactgtcatt ccctggccat gttgcaaaaca 1020
gcgcaattcc aagctcgaga gcttcagcct caggaaagaa cttccccttc cctgtctccc 1080
atccctctgt ggcaggcgcc tctcaccagg gcaggagagg actcagcctc ctgtgttttg 1140
gagaaggggc ccaatgtgtg ttgacgatgg ctgggggcca ggtgtttctg ttagaggcca 1200
agtattattg acacaggatt gcaaacacac aaacaattgg aacagagcac tctgaaaggc 1260
cattttttaa gcatttttaa atctattctc tcccccttc tccctggatg attcaggaag 1320
ctgmacattg tttcctcaag gcagaatttt cctggttctg ttttctcagc cagttgctgt 1380
ggaaggagaa tgctttcttt gtggcctcat ctgtggtttc gtgtccctct gaaggaaact 1440
agtttccact gtgtaacagg cagacatgta actattttaa gcacagttca gtcctaaaag 1500
ggtctgggag aaccagatga tgtactaggt gaagcattgc attgtgggaa tcacaaagca 1560
aatagtactc cagaaagacc ctgtctcaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1620
aaaaaa

```

<210> 34

<211> 450

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (291)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (382)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (404)

<223> n equals a,t,g, or c

## 21

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (439)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 34

```
acccacgcgt ccgccggcgc ggtctatggc tgcgacttct ctaatgtctg ctttggctgc 60
ccggctgctg cagcccgcgc acagctgctc ccttcgcctt cggcccttcc acctcgcggc 120
agttcgrgga akctctccct aggtcagggt ggagtgcagt gctgcaatca cggcttactg 180
cagccttgac ctcttgggct caagtgatcc tcccacctca gcttaaataga agctgttgct 240
atttctggaa ggaaactggc ccagcagatc aagcaagaag tgcggcaaga ngtagaagat 300
ggggtgggct ccaggcaaca aacggccaca cctgaatgtt gatcccgggt tggcgaaaaa 360
tccctgcaag tcactcctaa tntcctccaa caaaaacaaa gggnaagttg caatttggtg 420
ggaaatccac cagttgaana acaatttttt 450
```

&lt;210&gt; 35

&lt;211&gt; 960

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 35

```
atTTTTTTTT tTTTTTTTT tTTTTTTaaa acaacttctc aaattttatt aactcatgtg 60
gttaacatgg tattgtataa aaagaaaaaa aaaacaccac tcaatactta ctaagccttg 120
cagacagctc agagttgagg cagcatattg ggcatagaga tcataggatt tgtattatcc 180
cttgcaagat ggaactccaa ccaacaccag aattttccaa ttcaaatca gttttagtcg 240
agaccccgac ataattttta gaaaaaagat tggattgttg cttttctttt aattttccat 300
tcctatttag acaaattgacc agaggcaatg acaaaaagtaa ctgttttaaaa gggattttctc 360
tcagaagtt ttttctaaag gtttaagtcc aggctttcca tccttctctc catccttttt 420
catttttaaaa agaagggttt tggratwtgt caacctttac tcagcttgct atacaaagcc 480
actgcttttag tcctagacat aatgccagga ctcatctccc aaacttctgg tcttaataca 540
gttcatgctt ggttgctaaa gaagctcatg ttaatcccaa agtcagcaca atcccaacct 600
taaaaagcag acagcctgat tgcatactt acgacataca ccatcttgag gcaaaagaag 660
ccagtcagac accccttgte tgctacgtgt gagacacatc agcagttgag cctgaccctt 720
tcgcagagc tcactgtgca aaatcaccag cacaccactg caatccactg agctcaccgc 780
ctgtccagcc ataattggaag tcaattgaag gttatcattg taatagatga ttttccataa 840
gtaactaata aaaatgtttt ctttgatgtt tagacctact aacaattcag tctctccctc 900
tccatcctct cttaggggagc ctgtactttt aagcaaatag ggaagctaaa acctcgtgcc 960
```

&lt;210&gt; 36

&lt;211&gt; 530

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (78)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (362)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 36

```
taacaattca atatataatt acacaaataa ttttttaaata taatcaatag taaagactgt 60
tctgtggatg gtagtgnta atacattttc tattttgtac agtgatttta ggccaaacag 120
ctgctgattt taagaaaaca aaaggcctga aaccgcgtctt cgtgtctcct ccctccctcg 180
ccttctcctt tcttagctcc tctcctccag ggccagactg agcccagggtt gatttcaggc 240
ggacaccaat agactccaca gcagctccag gagcccagac accggcgggc agaagcaagg 300
ctaggagctg ctgcagccat gtcggccctc agcctcctca ttctgggcct gctcacggca 360
knccacctgc cagctgtcag caaggcctgg ggaacttcag ccctggatgc agggccttat 420
cgcggtggcc gtgttcctgg tcctcgttgc aatcgctttt gcagtcaacc acttctggtg 480
ccaggaggag ccggagmtgg gagtctggtt ggggaacaga ttggaaggta 530
```

&lt;210&gt; 37

&lt;211&gt; 538

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (41)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (502)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 37

```
gccgcggcca cggggcgagc gggccatggt gcgcggcagg ntcttcgggc tctcggtccg 60
ggacgtgcgc ttccccacgt cgcttggggg ccacggcgcg gacgccatgc acacggaccc 120
tgactactca gctgcctatg tcgtcataga aactgatgca gaagatggaa tcaaggggtg 180
tggaattacc ttactcttgg graaaggcac trwagttggt gtctgtsctg tgaatgcctt 240
cgccccacat gtgctcaaca aggacctcaa ggacattggt ggtgacttca gaggcttcta 300
taggcagctc acaagtgatg ggcagctcag atggattggt ccagaaaagg gcgtggtgca 360
cctggcgaca sggcgcgtct aaacgcgggtg tgggacttgt gggccaagca ggagggaaag 420
cctgtctgga attacttgtg gacatggatc ccaggacgct ggtatcctgc atagatttca 480
ggtacatcac tgatgtcctg antgaggagg atgccctaga aatactgcag aaagtcaa 538
```

&lt;210&gt; 38

&lt;211&gt; 1256

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 38

```
ggcacgagca ttaacaaaaa aatgtgcaaa cacactacta tgatttacca aaagactctc 60
tgcaagtggg aaatcattag ctctagtgtt gctctttgta acctcaggtc tttggggaaat 120
ggtgcagaat tagtattgct tccttctttc tgtgtgtgat aatgggtggg gaaggctagt 180
accatctctg tcatacatca aattcccata tgtgaataaa tttatgtatt tttactgcac 240
tctttttata gggtttatcat tcctgcacca acaacgaatg ccattattaa aactttatag 300
```

## 23

```

aaagtctcaa tatatggcac agtgcttcat ttcttttttt catctagagt gccttagcca 360
ttcttggcctt tctgccgttc cacaatatagc aatgtaaatt tgtcagtata atagagaatc 420
cacttatatt tcttcaacag ctattgggaa tatggttggg attacttcaa ctctatgtat 480
caatttgagg agaattgata tctttataag attaatccaa atcacagcat gtcaaaattt 540
ccttattagg gtagtttttaa tgtccttcaa aaacactgta ttttcttcat atagatctaa 600
gaaaactttg gtgttttattc ctaagaaatt tatagttctt gttttgtaaa tgatatctat 660
tcttaagtta cacttaaact tatttggtgc tgtatataga aatggaattg acttctatgt 720
acagcagttg caaactgata ttcatatgca gaaagtgaag ctagaccctt aatggataaa 780
agacttaaat gtaagacctg aaagtatgaa actactagaa gaaaacatat gggaaacact 840
tcagtatcct ggcctgggtg aagattttat ggagaaaacc tcaaaagcat aggcaacaaa 900
agcaaaaatg gacaaatagg attatatcaa actaaaaaga ttcagcacag taaaataaat 960
aatcwataga gtgaagagac aaccttcaga agatatttgc aaactattca tctgacaagg 1020
gattaatatt tagaacatac aaggacctca aacaactgag caacaacaac aaaaatatcc 1080
aattttaaaa atggggcgaag gagccaaata aacatctctg aaaaccagac gcaagtggcc 1140
aacaggtata tgaaaaaaa aaatgctgaa caccgcta atcatcaggaa atgcaaacca 1200
ataccacaat gagatattat ctcatwtggt ctattatcaa aaaaaaaaaa aaaaaa 1256

```

&lt;210&gt; 39

&lt;211&gt; 666

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 39

```

tggcacctgc aggactgcca agatctcctt ggcgctgcgg ggccattggc ggggatgggc 60
gggggagggg ggcctcgacg gtttcccatc cccctctggc aaccctaate ttctttctcc 120
atctggggccc tggggcgctct tccaccaccc aggcgggatg ctttaaaaaa aattgctttt 180
taaagtgtct gtcgttgaaa gaaattagtc ttacccttga agtcargggc gcgtcctcgc 240
aatacacatc ttgttaggga aagtgttcgg ctccagctak ggttctacaa ggcgtttctt 300
gttcaccgcc ggagggaagc aggcctccga gtgactgcct tctgaaagtc ggtcttgtaa 360
caattggatg ratgcctttg aagagccctt gtccctattc tatgcttgaa aacagcgtgc 420
agtcctaatt ttcaagaacc acgaccacat aaaaacattg ctcccttctt gctgctttga 480
aaacgacccc taaattccgt gtagaagttg ccaggctcgtc ttgacgtaca cttcgtttgt 540
atgatgtttg tctgtcaaat actgtgatgg aagagtgtat gcgggggagg agcaggggat 600
ttttaaaarc attttccggk cacctcagac tgggagatca tgttctttcc tgaaaaaaa 660
aaaaaa

```

&lt;210&gt; 40

&lt;211&gt; 1016

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (6)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 40

```

ctggcncctgc atcctcaaca tcttcaaagg gtacaacttc tcccgggaga gcgtggagag 60
ccccgagcag aagggcctga cgtaccaccg catcgtagag gctttccggt ttgcctacgc 120
caagaggacc ctgcttgggg accccaagtt tgtggatgtg actgaggtgg tccgcaacat 180
gacctccgag ttcttcgctg ccagctccg ggccagatc tctgacgaca ccaatcacc 240

```

24

```

gatctcctac tacaagcccg agttctacac gccggatgac gggggcactg ytcacctgtc 300
tgtcgtcgca raggacggca gtgctgtgtc cgccaccagc accatcaacc tctacttttg 360
ctccaaggte cgctccccgg tcagcgggat cctgttcaat aatgaaatgg acgacttcag 420
ctctcccagc atcaccaacg agtttggggg accccctcac ctgccaattt catccagcca 480
gggaagcagc cgctctcgtc catgtgcccg acgatcatgg tgggccagga cggccaggte 540
cggatggttg tgggagctgc tgggggcaca cagatcacca cggccactgc actggccatc 600
atctacaacc tctggttcgg ctatgacgtg aagcggggccg tggaggagcc ccggctgcac 660
aaccagcttc tgcccaacgt cagcagctg gagagaaaca ttgaccaggc agtgactgca 720
gccctggaga cccggcacca tcacaccag atcgcgtcca ccttcatcgc tgtggtgcaa 780
gccatcgtcc gcacggctgg tggctggcag ctgcctcggg ctccaggaaa ggcggggagc 840
tgccggctac tgagtgtcc aggaggacaa ggctgacaag caatccaggg acaagatact 900
caccaggacc aggaagggga ctctggggga ccggcttccc ctgtraagca gcagagcagc 960
acaataaatg aggccactgt gccaggctcc aggtgcctcc ctggcytgtc tcccc 1016

```

<210> 41  
 <211> 423  
 <212> DNA  
 <213> Homo sapiens

```

<400> 41
agtgagctgt gattgcaaca ctgcacttca gcgtgggcaa cagagtgaga tcttgtctca 60
aaaaaaagaa ataatactag tttttgtttk tagattttgt atcctgaaac tttactgaat 120
gttttttagt tcgaacagtt tttttggtgg agtctttagg attttctcta cttatgatcg 180
tgtcatctgt aaacagagac agttaacttc ctcccttccr atttagatgc cttttctttc 240
tcttgccata ttgcctaatt acagcatgtt cctattctgt aaatgttcaa tgaactagar 300
aatgattctt gggtagttaa tattgtcaat gttgatgaac tcttttcctt cgctgaaagc 360
agctactttg ttggagggtt caattctgcg tggcaatttg cagcatttct agtgggtactg 420
ctc 423

```

<210> 42  
 <211> 961  
 <212> DNA  
 <213> Homo sapiens

```

<400> 42
gcctctacca cctcagttac agacaccacc aagggtcaaac agtgtatttg ctgtcaacca 60
agctgtgtca ccaaactttt cacaaggatc tgccataata attgcctctc cagtccagcc 120
tgtactccaa ggaatggtag ggatgatccc agtatctgtg gttggacaga atggaaataa 180
cttttctact cctcctcggc aggttcttca tatgcctttg acagcacctg tatgcaatag 240
aagtatccct caattccccg tccctccaaa atctcagaag gctcagggac taagaaacaa 300
gccttgatata ggaraacaag taaataattt ggtggattcg tcaggtcatt cagttggatg 360
tcatgcacaa aaaactgaag tttctgacaa aagtattgcc acagatcttg ggaaaaaatc 420
agaagaaacc acagttccct tcccagaaga gagtatagtt ccagctgcta aaccatgcca 480
cagacgtgta ctctgtttcg acagcactac tgctcctgtg gcaaaatacg aggggcaaaa 540
ccataagrtg gtgtcccaaa acaaagaaag gaatgcagtc tcttttctta atcttgactc 600
acccaatgtg tctctcacct taaaaccccc ttctaataat gctatcaaaa gagagaaaga 660
gaagcctcct tcctctaaga ttttatctaa atcggaaaagt gccattagcc ggcataccac 720
cataagagaa actcaatcag aaaagaaagt ttcaccaaca gaaattgtgc ttgaatcttt 780
ccataaagca acagctaata aggagaatga attatgcagc gatgtaggaa agacagaaaa 840
atccagaaaa ttcaaaacta tctattgggc agcaaaatgg gggtttgca agtgagaaat 900
ctatagcttc actgcaagaa atgacaaaaa aacaaggcac atcttcaaac aataaaaaatg 960

```



t

961

<210> 43  
 <211> 545  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (12)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (34)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (142)  
 <223> n equals a,t,g, or c

<400> 43  
 ccaccgcggt gncgaccgct ctagaactag tggntcccc gggctgcagg aattcggcac 60  
 gagttggagt cctttgctgt tcccaatttg tggaagagtg aagacatcac ccaaatcgtg 120  
 gccaaactatg ggctcatatg tnttactcgg gctggaaatg atgctcagaa gtttatctat 180  
 gaatcggatg tgctgtggaa acaccggagc aacattcacg tggatgaatga atggwtcgt 240  
 aatgacatct catccacaaa aatccggaga gccctcagaa ggggccagag cattcgctac 300  
 ttggtaccag atcttgtcca agaatacatt gaaaagcata atttgtacag ctctgagagt 360  
 gaagacagga atgctggggg catcctggcc cctttgcaga gaaacactgc agaagctaag 420  
 acataggaat tctacagcat gatatttcag acttccatt tggggatctg aaacaatctg 480  
 ggagttaata actgggggaaa gaagttgtga tctgttcct aaactaaagc ttaaaagttt 540  
 agtaa 545

<210> 44  
 <211> 377  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (301)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (347)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature

&lt;222&gt; (359)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 44

```

cgatcacccc cgaaccattt catcacgtat tcttcagtgg ctggacgagg agctgcccga 60
cctgtccgtg tctcgagaa gtagccactt gcactggggc attccgggtgc ccgggggatga 120
ttcgagacc atctatgtat ggctggatgc cctgggtcaac tacctcactg taattggcta 180
cccaaattgct gagttcaaatt cttggtggcc ggccactctc atatcatagg taaggacatt 240
ctcaaattcc atgccatcta ttggcctgcc ttctgttar gggccggcat gagcccgcca 300
nagcgcattc gtgttccatt cccaatggaa cagtctgtgg gccaaanatg tccaagagnt 360
tgggcaagtg gtggatc 377

```

&lt;210&gt; 45

&lt;211&gt; 440

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (387)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (416)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (436)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 45

```

ttggacatcg tggccaactc tatcaagacc acaaatacca cttacaatta attttaaatt 60
attcatctgt acatagtttt ctaaaatgta tataattcaa acagagcatc ttgtaactga 120
agacacacca tatctatgat atcgcattag tccatgtggg gaaaagaaag atcagattgt 180
tactgtgtct gtgtagaaaa ggaagacata agaaactcca ttttgatctg tactaagaaa 240
aattgtttct gctttgagat gttgttagcc tataacttta gcccactc tgtgctcaca 300
gaaacatgcg ctgtaatgga tcaaagttta atggatttag ggctgtgcag gatgtgcctt 360
gttaacaata tgtttggcag gcggtangcc ttgggtagaa gtcacgggcc attccnccat 420
tccccggttt aaccnngggg 440

```

&lt;210&gt; 46

&lt;211&gt; 525

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (345)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 46

```

gtccggctgg gccgggacaa aagccggatc ccgggaagct accggctgct ggggtgctcc 60
ggattttscg ggggttcgtcg ggcctgtgga agaagcgccg cgcaacggac ttcggcagag 120
gtagagcagg tctctctgca gccatgtcgg ccaaggcaat ttcagagcag acgggcaaag 180
aactccttta caagttcate tgtaccacct cagccatcca gaatcggttc aagtatgctc 240
gggtcactcc tgacacagac tgggcccgtc tgctgcagga ccaccctgg ctgctcagcc 300
araacttggg agtcaagcca gaccagcttg atcaaacgtc gtggnaaaac ttggtcttcg 360
ttgggggttca acctcactct ggatggggtc aagtcctggg ttgaagccac ggttggggac 420
aggaagccac agttggcaag gccacaggct tcctcaagaa ctttctgaty gagccyttcg 480
tccccacag tcaggytkag gagttctatg tctgcatcta tgcca 525

```

&lt;210&gt; 47

&lt;211&gt; 414

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (403)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 47

```

ttagaaagar agggggctgg gggccgagac ttctgggtcc ctgtatgttg cagagggttg 60
catgtcatct ccatggagaa ggctgtgtac gctgtcacgc aatcccttgt aagaggccag 120
gcccctgggg gaggaggag cagctgtggc tcacacagcc ccaggaaacc acctcttct 180
tcagtgaagc agatagatag agaatcccg gacagtgaca ggcaagtga tagccagata 240
gaaagcattt ttgtgtaata actaattttt gtttgcttct ctctctctct tccccgccct 300
ccccatccgg attcccgtgg ctgtgtgcat ctctgscgtg tgtcccatg tctgcccga 360
gtgcgcttct ccgagaaggt cactgtccat tcctgggtgt ctnggcaagg ccgg 414

```

&lt;210&gt; 48

&lt;211&gt; 323

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (11)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (274)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (321)

&lt;223&gt; n equals a,t,g, or c

28

<400> 48  
 tcgggtccgg nattcgccgg tgccggggac agaaacctcc tgccttctta gttcataacc 60  
 ccccttaca ttagattcta accctgtggt gatttttaggt tgggatttgg gcgcctgcag 120  
 atggctccga agccagcctc ttgtgatccg agccacttct ctggcactcg gagcgctggc 180  
 acccgcgagg cccttggttc accggaccgc ctgggaacct ggccggggtc tctggcagcc 240  
 tcccagggct gaggttcaga ctctgttccg cctnaccag gtccacacct ggatagggct 300  
 gggagttgag gcttggtttt naa 323

<210> 49  
 <211> 841  
 <212> DNA  
 <213> Homo sapiens

<400> 49  
 tcgaccacg cgtccgsaga tttcagcctc acatactaag taaatactga taaataagga 60  
 aattagaaat ttagtattca taattaaata tgctctaaaa tttcckrtac ttttatttcc 120  
 tgtttattct taggtagatt ggaaggggga aacagtctgt tctccctaata taaatttttt 180  
 ctaataacga ttagtagaat atggacattc tatatgacag tgacattaaa agaggctctt 240  
 tggaagtata tacattatta acataatgtg tacaagtcct tttgaaatga caactttaat 300  
 gggtttcagc tcttttatct agagcttgag ataattcaag ctgagttttt cagggcatat 360  
 cacaacggca aagtgttcag cagtgggata tcaatgctta tttacatttt cctactgcta 420  
 tttatataaa atgttattcc attcagagga tgctttttat cccacatta aagcacagat 480  
 cattaagcaa taaaaaccaa attgtctgtc attcaaatta taactgcagt tatttttgca 540  
 tggttaagagt gaggtgctaa ttttgtgtga gatgaacttt gtaaactact ttgggaaatg 600  
 ttctttggaa gtaaggtttt ttctccttta gtcttatgct tccacttttg tctcagattc 660  
 acaatccatt aaaamawggg gaaaaaagaa aargtaaaat tgagagactt ttgttagagg 720  
 agctatttgg aatgaaccaa cattycasat ttcccaaaat gtaagttagg aagtctccat 780  
 kgycyckgcc attaccaaaa tacactgkta ctatcttaat ctcaagagtg tcattacagt 840  
 g 841

<210> 50  
 <211> 534  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (423)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (430)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (524)  
 <223> n equals a,t,g, or c

<400> 50

## 29

```

aggaaattta gaaaatgatg aattcttgtc catttttgta atcaagattt taggaaaaac 60
agaagtacat ctatctttat gaaattttgg gcaggttttt gtgtatcaat attttgtact 120
tttagggaat attttatttt ttagttattt gtgtcaaatt ataattataa aaggtagacg 180
agaaaaatata ccatgttttt atatagggttc acacctgtac ttaggaggga ccctgtccat 240
ctatatactt tttgtataaa attttaaaat gttaaagatc cacaagggtc taataaaaatg 300
attctatagc tagaaaaacc attaccttcc cagtgggttg cactaaaata tacctgggaa 360
aaggaaccta gaaagactgg taactaatgc ctggaaatgt tctatattga atgtaccatg 420
ccnctggtnn gggaaaaatg tactaataat gggaaatggga aataaaccca gaaatccgaa 480
gttaattcca gcctaaaaaa aaaaaaaaaa aaaagggggg gccncccta gggg 534

```

&lt;210&gt; 51

&lt;211&gt; 317

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (222)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (250)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (265)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 51

```

ggcacaggaa aaagcacttt cttaagccta cagtatcaga tcaatgggga aaacaacaga 60
aaactaagag gagaattttc ccgttaattt tcttgcagaa aagtataagt ctaattgccc 120
attgccataa attttgtctt gtactcagag aagcaacatg cactgggtca ttttatgtgc 180
aaagaaaaga tttcaccatt aaaaaaatta acttggctag gnatgggtgc tcacactggt 240
gaatcccagn cactttgggt ggctnaaggc agatagactg cttgaaaccc aggaattcaa 300
gaccagcctg ggacaac 317

```

&lt;210&gt; 52

&lt;211&gt; 1789

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 52

```

ggcacgagga aacggacaac aatgttggtg ccaaaactgg atcaggctac cataatcttt 60
tttcttacat tccacttttc tatcttttcc aaatatcca cagtatcat gtattaattt 120
ttctcttatt ttgatgttgc aaatatattt tttattatgg aaaacggcaa gctacatatg 180
gggaaaaaga aaaattgaaa ttatgcaatg gcctaccact caagagataa ttattaagat 240
tgtggtgtac ttttttctat atactttttt ttaaaggaaa ggatcttact ctgtcgacca 300
gcccctcacc tcctttgact agctgggatg acagcacatg ccaccatata caagtatttt 360
tgtatttttt gtagagaagg ggtttcatta tgttcaaact cctcagctgg cctgcttgat 420

```

30

```

ccgatgcttg ttagccttga catttacaat gaacacaagt gtgttgccat cttctgtctt 480
cttcacagac aacttagtag tcagggggaac ttgatgatgg ccaagtgggc aagctcctca 540
gggctgtctt ccgtggatac ttgagctgcc ccaggagcca cagcgtctca ggcagctgaa 600
aagtgagtga catgtagggt gtgtgtgtgt gtgtgtgtgt gtgtgtatgt gtgtgtgtgt 660
gtagctgtaa cacctcagcc ttgcctcctt ggccttcaca gcccttgctt tagctttggc 720
tttgagagag gcagaggctc cctcttttgc cctcactgtt atcttggtga aaagccagtt 780
tggcagtttc tttttttaa aaaatgcaag tatcataatt cagcaatcac atttgggggc 840
aatttatccc agagaaaggg aaatttatgt tcacataaaa acctgaatta acttcaaggg 900
aatgttattt aacaaacagg ttttctcact taactgatta tattcttgat ggatacacia 960
attaaatctt aatacaatat ctccagtgga tcctccaaag ttgtatctgt tttcatgggc 1020
cagaatgagg gaaagtcatt ctggccattc tcttttgcag agaaggatcat tctcttttct 1080
atatgaggag catctctcaa ctgcaagggtg cagctcaaat atctgtctat gtatagatac 1140
gactttcaaa gtctagatag gaatggcctt aacataccat ccacatttta tggaaaatcg 1200
cttgtttctc ttttcccctg tcttaatctg tttgtgctgt aaacaaaaca aaataccaga 1260
gactggataa tttataaaca gcaggagttt atttctcaca gtttcagagg ctgggaagtc 1320
caagatcaag gtgccggcag gcttggtgtc tagggaagga tcattcctta tagatgttac 1380
catctagggtg tcttcacatg gtaaagggaa ggaagggcaa acagggacct agttggtccc 1440
cgccagacct ttcataagggt cactagtccc actcatggag gctctacccc catgacttga 1500
ttttttccta aaggccccac ctcttgacac tgttgcatg aagattaaat ttcaaatga 1560
attttgaggg gaatgcaaac attcaaaca cagcactccc tcactatag atttctacaa 1620
ctttcagatt attgcagcaa gtggttccat ctgtaaata cttggctagc ttatgtgtgt 1680
tgtctctctt ccataacaca tcaacccaag atttccaaca aaagaataat aacttaaaac 1740
aacaacaaaa aaactcactc acacaaagta tgtgtataag caggttgta 1789

```

<210> 53  
 <211> 654  
 <212> DNA  
 <213> Homo sapiens

```

<400> 53
aatteggcac aggcattgggt gtccctctgt actcagaatg ggttcagsc aagtcggtra 60
aratggatgt tggcaaaata ggaggatacc ctcatctgct gaatggggga cctgctctga 120
gcctgcccag kggccaggcc tgctccaggt taaactggac ggaaggcca ggtctcagtt 180
tctttcaacc aggagaggcc gctgcctaga gccctcccc accttttctt ggatgggtga 240
ggcaagccag gagagcaagc agtgttgctc tcacgggagg aggactgagc gactgggaaa 300
actcggctct acatctcacc cagaacggct tttagaaaca ccacagctgg agagtcctgg 360
ctgagccttg ggagtttcag ctctttggcg gggtgcccag gtgccatgcg atcagcgaag 420
cctgcgagtt ggcaggactc tgaggtttcc tgcagaccat gccatgagat tgaagggtgcg 480
gggaaataaaa gaaaaatcac catttaggag actccattct ttccctacaa cccagctgtg 540
gtcccagaga tcagggggtg ttgccagggt tggctgggga agggctctggg ttcacaaact 600
caccggcact ctttagtccc cgtataacat ggtggttaag gataaagatc ttga 654

```

<210> 54  
 <211> 334  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (154)  
 <223> n equals a,t,g, or c

## 31

&lt;400&gt; 54

```

ggcacgtagg ggatgcccac cgccagtcaa aggggttgggg gtggtctctg caccttaagt 60
actaacctgc cgcccacgcg cctcctgacc acagcacccc gtcggctttc taattctgtg 120
agctgccctc gtgggcgtgg cctccctgtg gagntcccca tgtgcctccc cttgggtccag 180
cctgcagcta ggaagtgggt cacagcgacg gggctgggct gggccaggcc aggctccggg 240
agatgtggaa ttggcgaaac aactgcccc atagtatcct ccgcctaggr ctccaagagg 300
tggaattgg ggcactacgg ccgggtaagg cagt                                     334

```

&lt;210&gt; 55

&lt;211&gt; 474

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 55

```

tgcaaacatg atggatgggg aaagcatagt aactgtactc accaacaaga tgctggagtg 60
acctgctcag atggatccaa tttggaaatg aggctgacgc gtggagggaa tatgtgttct 120
ggaagaatag agatcaaatt ccaaggacgg tggggaacag tgtgtgatga taacttcaac 180
atagatcatg catctgtcat ttgtagacaa cttgaatgtg gaagtgtctg cagtttctct 240
ggttcatcta attttggara argctctgga ccaatctggt ttgatgatct tatatgcaac 300
ggaaatgagt cagctctctg gaactgcaaa catcaaggat ggggaaagca taactgtgat 360
catgctgarg atgctggakt gatttgctca aagggascag atctgacctg aractggtaa 420
tggagtcact gaatgttcag gaagattaga agtgagattc caaggagaat gggg          474

```

&lt;210&gt; 56

&lt;211&gt; 367

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (250)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (252)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 56

```

ccggcctcaa gcaatcctcc cactggcctc acaatgttgg gattacaggt ataagccact 60
gcacacggcc ttactatgct atcaattcca tatatggaaa ggtgttttcc ctttcagagc 120
tctttaaagc tctgcagaag atttacatgt gtttatagag ctaagagaaa tcagggcatg 180
gaaattgagt gtgtaataaa aattaaactc ttcattgtat ataatcatgc ataacttcta 240
tcttcattcn cnggaagtgt cctagagcac catcacagct aggaagcttc catcatggat 300
taccttattt cccaaagcaa gtactccaat aattgtctca agagaggaag gacaactggg 360
taccagc                                     367

```

&lt;210&gt; 57

&lt;211&gt; 564

&lt;212&gt; DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (542)

<223> n equals a,t,g, or c

<400> 57

```

caaccccccta cagatatcaa gggaccacta tacacattag gatgatctat attgaaatct 60
acatggaaca gagtgggact tctaattgta tgacttcaag attttgcttt gtttaaatta 120
ataactgttt tcagaattaa gtgcttaaaa acaaatttga ttgaaaagtt caagacaaga 180
attttgctct ctatggctgt tccatataaa tttgatgggt gattctgaat gtaaattgact 240
gaagaattaa aaaataagaa attccttttt aaaaggcatg cctcttgac tgtgaacaag 300
acagtagtcc cttaaaccat gaatatgtca gtgttctatg gattacgaaa ttagtaatgt 360
tgcttagccc aaacgtgttt tttaaaaagt atagttttgt acatctcyaa gttatcaaac 420
ttcaaaattg agaacaaatt taaaagtcca tatatgcaac tctagtaagc acttaatagg 480
ttacatagca ctgggttaaga acaattaatt ttgtttctat attattacta attattatta 540
cnaatcaaaa aacactgtga taag                                     564

```

<210> 58

<211> 444

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (358)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (382)

<223> n equals a,t,g, or c

<400> 58

```

ggcagcagggg aaaaccataa ctgcctctta atttaacata gaataatata tagttctgta 60
tttttttttaa agtgagctta atgggtaagt attttttata tgcttttagct atagctaaag 120
aaaactgata cttaacaaag ttgaatagta ttattcactg gtgctcctaa aatattgttt 180
ttcagtgtaa aatatgcata tcttctatat ttaatatgaa agtcttgaaa tgtatcagac 240
agaagggkat ttcagtttgc aaataatgag caatgtagca attttaacac atttcataaa 300
tatatatattt gtcattgggtg gagagcacca tttgttgttt tgaatatact ttaaaggnaa 360
gaggtacaag ggacataaat gntgagatta cctacaggat ggaaatagca gtacagttcc 420
attggtagat attttgaaat gttt                                     444

```

<210> 59

<211> 347

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature



<222> (327)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (328)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (340)  
 <223> n equals a,t,g, or c

<400> 59  
 ttgagctcta aatgcaaaac tcttttatac tgaaaaaaca cttaaagyag ttttgtgtgg 60  
 catcacagtg atttgtcatg aaaagccata tatggggggac atgctaaaat ggcttctgaa 120  
 tgaaatacga cagcagagaa agatgccact gaaatgctga aattatcttt gctgagcagc 180  
 ttttgaatgc taagggttcc agtatgtgac ccaaagaagg agttgtctca actccttggt 240  
 acagggttca ttcaaaccac caagctgtga gagtgtgttt atttttaatt ttttaaaagg 300  
 tattttaattt ccaaccacac ttcttanntt tttggaaaan gacaatt 347

<210> 60  
 <211> 322  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (245)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (321)  
 <223> n equals a,t,g, or c

<400> 60  
 agctggggcc aaaaatagac cagaattatc tgctacttga atgtttggca aaactctcct 60  
 agaaaactga gtctgatgtt tgatttgtgt aaagacttct ttaacttttc taactcaatt 120  
 ttactaagt tataggacta ctcagatctt gtttcttttt tgctcaattt tgggtcaattt 180  
 tgtttttgtc tatgtcacct aagtttycaa atgtattggc atgaatattt ycataatatt 240  
 ccctnattat cttttacatt tctgggggtat cttagcggtg tttccctttt tatccctaaa 300  
 atgttttatcc atgttttctt nt 322

<210> 61  
 <211> 834  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature

<222> (793)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (810)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (814)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (834)  
 <223> n equals a,t,g, or c

<400> 61  
 gatatgatgc ccctccttca taattatgta acagttgata cagacacact tctgtctgac 60  
 accaagtatc ttgaaatgat atacagtatg tgcaaaaagg ttcttacagg agttgcagga 120  
 gaagatgcag agtgtcatgc agcaaaattg ttagagggtca tcattctgca gtgcaaaggg 180  
 cgtggcattg accagtgcac tcccttattc gtggaagcag ccttagaaaag actgacaaga 240  
 gaggttaaga caagtgaact tcgaactatg tgtctgcaag ttgcaattgc agctttgtat 300  
 tataatccac acctactact cmatacctta gaaaatcttc gcttccctaa taatgttgaa 360  
 ccagttacma atcattttat tacacagtgg cttaatgatg ttggactggt tcttggggct 420  
 tcatgacaga aagatgtgtg ttctcggact ctgtgctctt attgatatgg aacagatacc 480  
 ccaagtttta aatcagggtt cyggacagat ttgcccggcy tttatccttt tatttaacgg 540  
 attgaaaaga gcatatgcct gccatgcaga acatgagaat gacagtgatg atgatgatga 600  
 agctgaagat gatgatgaaa ccgaggaact ggggagtgat gaaagatgat attgatgaaa 660  
 gatgggcaag aatatttgga gattctggct aagcaggctg gttgaaagat gggagattga 720  
 tgaaagattg ggaagaaaga tgatgctgaa agaaactgct ctggaaaggc tattcccaca 780  
 atcattgatg atnaaaaaat aaccctgtn gatnaatttc caaatatttt aaan 834

<210> 62  
 <211> 1796  
 <212> DNA  
 <213> Homo sapiens

<400> 62  
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 actagcttta cctctttgac cccactgtat tattgtctag cccagttcag ctgaatcttt 180  
 caacacaaaa tatacaggga accccttcct ggggaacttc ctttgttatt gaggtcttcg 240  
 ctgatggctt ctccatttg atactcagtc tcagtcacag taggattacg gaatcttttg 300  
 ccagagtatc aatctacatg ggtgctacac attactgaaa aaaattagga acatggtgct 360  
 agttaattca agtcttcag taaaacttct tctatcatag tggacattaa aaaaaatctc 420  
 tctgcaaaagtc gattgaccc tacctctagt agatgaatgt tgaacaagta gcctatctag 480  
 gaagcaagtg actagcatcc atgggcatcc cacagggtgt agtccagccc cgatcttggt 540  
 gggtgggatt gatgttctg ccaagtccct ccgtttcatg ttcaggctct gcctatgttc 600  
 ctggtgtctg gtacctgatt ttcaggatg ctgacattta cttcttgccc acaacaccat 660

## 35

```

ataccctaag tcttgccaac atctttgaat gtcttctgct ggtctgtctc tcctccgttg 720
ttcttttact atgtcccaag tgcattgctt gtccagatc tgccctaagtc tcaggatamt 780
gatttttagct ttttactagg tcctgacatt cccgtagttt cctcttacct ttctggacat 840
gccagacaaa ctctgacctt aggttctgtg aaaactggta cctgcagaat tcctcagtg 900
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agcagtgggc agagggtgca acattttattt gggtatagga cacctttgct actggagcat 1020
cttgtagggt aatgtagtcc agaaccatgca tggagaaatg ctgccataga gtagtagtga 1080
catttgggac ttgaaaaaaaa tcttaagagc aggtataatt ccctcaacaa cagaagaaca 1140
tcagtgtctt agaattgttg attttgaact ttcttgatgt tttctctgcc gttctgtagt 1200
gttattctaa ttaaaatctt tcctctaaac tctgtctctt tttttccaat tgagcaaatt 1260
cggcatttat tgaggcccta ctacatgtca tatgtgttct tatttgctgg aaacacaaat 1320
gtgaatatgg taggcctgcc cttaaacaaat gaattacagt gtaaaatgaa ctttttataa 1380
agctggctct atatcaatct aattattttg tttttcttca tttcaggcct aagacagctt 1440
tattttcttt ccactccaaa taatgaagaa tccccttagg gcaaagaagg aatttctgag 1500
catgttataa aaaaatagaa aataggataa gttgcgtgaa gatttaatat ttctatacat 1560
caaacctac cataaacaaa attaaaaggc aaatagtaaa cttggaagaa catttgtaac 1620
ataaaagaca aaagttaaat atcataataa aataagcaca tagtagcttt tagtaaatca 1680
ttgctgaatg aatgaataca tatatgaatt caaagcaatg aaaaaatcac cccaggaaaa 1740
gatgtaaaca tttgacatag gacaagtcac caaaaaaaaa aaaaaaaaaa ctcgta 1796

```

&lt;210&gt; 63

&lt;211&gt; 1376

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 63

```

ggcacgagtt ttggactagg tcgcacagtt attaaaacaa cttttaaccc tcccccttca 60
cacacatata tatcagggttg ttttctagtt aaaaacccaa gtagctcaga ttctacttta 120
atgtcagtg cagatttgcat tgaatcatgc cattatgttt tttctcattt ttatgctgtt 180
gggtcttagt ttttaaatg atataaagaa ctcagcaatg gttttatttt ctactcatac 240
ttagggttta ggaaacacta ccactagtta tcatttaatc aacttcaatg gtctactgaa 300
acaaaaatgg taacttttca ttagtggtt atttagagtt atagtagttg tttccagaaa 360
acacttctc acaattgtac ttcccaatca aatcatgtga tcatacagtt attcccatga 420
aaggcagaat gtttgtttca aaattaatct agttttctgt acattttaat ttgagaaggt 480
gacaactggc tcttttccag tcttcttca tgtcagtttt ctgatagacc actattggca 540
aacagtatct gtcaactacc aaatgtgtaa aattttctgt atttcacttt gtcttatttg 600
taaatagtga actaaaactt ttggcagatc agcaacattt gctgagcctg ttttttaagc 660
taatgtgtat tcttactaat gttcctatca agaattggatt tgtaatatat gctgtctatt 720
tctaattgtt acattcatat tttgagggtt tatcttattt taatagagaa cagacttctc 780
aaaaaaaaat cagaagcagc ttattattga aatatcgaaa tattgaaata aaccgggttg 840
ggtagatta ctcatctgtc caccaagtgg gacatttgca tggactgggg gcttaaagga 900
cttagaagag acctgtaagt aaatcctgaa aatgagccaa tccccacttg aatggttact 960
ggagtaaacc cacctttacc accccaatta cagcacccga ggccgataaa ccaacttggc 1020
tctgggtcat ttttcttttc ttcatattgt atgctcagat tcaaaatgtg tgttctacac 1080
tggtacaggc ttctcttttg tttgattaaa gatttttagt ctacttttgt atggacacat 1140
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gatttgtggc aaatcattta tttgcctttt taaaaattca ttttaagcag tcagagagta 1260
gactactcag aaaattattt cacgtaattg tctaagaggt caatattttt taatgcatat 1320
tgaatcaaat aaagtgtctt aaagaaatta ttctccaaat aaatttttaa aaaaaa 1376

```

&lt;210&gt; 64

36

&lt;211&gt; 574

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 64

```

ggcacgagct gaaaggtggg ggaaggggaac gtagacctag agaggggaat tcttacagaa 60
atcctctttt tttggtcctt tctatttttc agtctccggc agcctcttgg tcatgaaagc 120
cctcagattg tcggcttccg cctctttctg ccttctgctg atcaacgggt taggggcagc 180
accccttggg cgccctgagg cgcagctcct cctctcagct ctgagcataa agagccggta 240
gccggggacg cagtggcccg gccaaaggat ggcagcgccc cagaggtccg aggcgctcgg 300
aattccgagc cgcaggacga gggagagctt ttccaggggc tggatccccg ggcgctggcc 360
gcggtgctgc tgcaggcact cgaccgtccc gcctcacccc cggcaccaag cggctcccag 420
caggggcccg aggaagaagc agctgaagct ctgctgaccg agaccgtgcg cagccagacc 480
cacagcctcc cggcgccgga gagccccggg cccgcgtccg cctcgccctc agactccgga 540
gaatgggccc gaggcgagcg atccctccga ggag 574

```

&lt;210&gt; 65

&lt;211&gt; 603

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 65

```

cccacgcgtc cggctggact gttttgatct cttttaattg ttctgacaga tagttgggga 60
tgagagccga ataaggtttg cctgaaataa ctgacactat ataatttctg ctttggcaaa 120
tactaagttc taacttgtca ttccctggtag aacaagcttt atttttcgag cctagcaatg 180
atctagaagc agatgttatc tcagtgcctt ttgcaatttg ttgtgtgggt tttttttttt 240
ttaaagccac acaataattt tggaaaacaa tgtatgggta gaacatgtgt ctgttaattg 300
cacacaaaac cacttttaat gggtagagag ttaaatttga aggaataagt tcataatact 360
gaagctagaa ccaagcagaa tctgtttttt tctgaggagt atcggttagc taaatgtgat 420
tataaacata gtacacttga tatatggagg cagtgcagc tatttttaca aaattttaat 480
ctgcaaatgg attcaacatg tttatgggtt attaaaattg tctgatttct taggttcttt 540
atagtacacg tgttgaaaat aaatgattaa gaattgtttc aagaaaaaaaa aaaaaaaaaa 600
aaa 603

```

&lt;210&gt; 66

&lt;211&gt; 1772

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 66

```

tcgaccacg cgtccgggag gatccccagc cgggtcccaa gcctgtgcct gagcctgagc 60
ctgagcctga gccgagccgg gagccggctg cgggggctcc gggctgtggg accgctgggc 120
ccccagcgat ggcgaccctg tggggaggcc ttcttcggct tggctccttg ctcagcctgt 180
cgtgcctggc gctttccgtg ctgctgctgg cgcactgtca gacgcgcga agaatttcga 240
ggatgtcaga tgtaaagtga tctgccctcc ctataaagaa aaattctggg catatttata 300
ataagaacat atctcagaaa gatttgtgatt gccttcattg tgtggagccc atgcctgtgc 360
gggggcctga tgtagaagca tactgtctac gctgtgaatg caaatatgaa gaaagaagct 420
ctgtcacaa caaggttacc attataattt atctctccat tttgggcctt ctacttctgt 480
acatgggtata tcttactctg gttgagccca tactgaagag gcgcctcttt ggacatgcac 540
agttgatata gagtgatgat gatattgggg atcaccagcc ttttgcaaat gcacacgatg 600
tgctagcccc ctcccgcagt cgagccaacg tgctgaacaa ggtagaatat ggcacagcag 660

```

37

```

cgctggaagc ttcaagtcca agagcagcga aaagtctgtc tttgaccggc atgttgtcct 720
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gaactgactg gggttttgctg ggtttcattt taataccttg ttgatttcac caactgttgc 840
tggaagattc aaaactggaa gkaaaaactt gcttgatttt tttttcttgt taacgtaata 900
atagagacat ttttaaaagc acacagctca aagtcagcca ataagtcttt tcctatttgt 960
gacttttact aataaaaaata aatctgcctg taaaataaat taaaaaatcc tttacctgga 1020
acaagcactc tctttttcac cacatagttt taacttgact ttccaagata attttcaggg 1080
tttttgttgt tgttggtttt tgtttgtttg ttttggtggg agaggggagg gatgcctggg 1140
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ccttctattt tgcagtttca tttatatttt gcagtgtagc cagcctcatc aaagagctga 1260
cttactcatt tgacttttgc actgactgta ttatctgggt atctgctgtg tctgcacttc 1320
atggtaaacy ggatctaaaaa tgcctgggtg cttttcacaa aaagcagatt ttcttcatgt 1380
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agactaaaca tagtcttggg gtgtgtgggt ttactcatct tctagtacct ttaaggacaa 1500
atcctaagga cttggacact tgcaataaag aaattttatt ttaaacccaa gcctccctgg 1560
attgataata tatacacatt tgtcagcatt tccggctgtg gtgagaggca gctgtttgag 1620
ctccaatgtg tgcagctttg aactagggct ggggttgtgg gtgcctcttc tgaaaggtct 1680
aaccattatt ggataactgg ctttttttct tcctcttttg aatgtaacaa taaaaataat 1740
ttttgaaaca tcaaaaaaaaa aaaaaaaaaa aa 1772

```

&lt;210&gt; 67

&lt;211&gt; 1829

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 67

```

cggcacgaga ttggagccta tttagtggat tttatgcagc caaagatggt tcttgttgtt 60
gttgttgttc ttgcttttaa ctaatttgcc tcccaggaga cagttgaaat gtctagagac 120
attttgatta ttatgcctgg caggacgcca ctagtggcat ctagtggatg gagggtaagg 180
gtgctgctaa gcgtcctccc atacacagga cagcaccccc cacaaagaat tatccaaccc 240
caaatgtcag tagtgctgag gctgagaaac cccactctgc tctctaacca aaattagaca 300
cagaaaagtg agacattcta ccaccctgac aacatcaatg gcttttgccc atttaaaaca 360
agaaaagagga atatgtatcc aacccaaaac aacatcttaa cattctttct aataggcttt 420
tgcaaaaaata gttcatattt tataactgtc ttgcagcatg ggggtataagt gtaatcattg 480
taaaaaatgaa acctaatacat tgtaaaaatg aaacctaata atggtaaaaa tgaaaagagt 540
gcctcaaaac atctgaagtt cttagcaaaa ggcagcctgt cttcagtggg cacttttgga 600
tgagggcagg actaggggat cagtaggagt gagaacaaag gtcagaaaaa tgagtacaca 660
gcacatgtat actgattaat ttctttcttt ttctcttctt ttgatggagc aagactgtaa 720
cagaagcctg agagtgagga agggcttttg caactattac tgtagacaca gtagtttact 780
caattttatg aactcttagt cctgggctgg aattcacgcc tctgctggaa ttgcacagac 840
aaaacgtgct tgcgaggagt aaggtggcaa caaaagaaaa atgcaggcaa aaacacgcct 900
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cttttttctt ctgggaacac aatgctactt tctgtatttg ctgagtaatg gccccaaaag 1200
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acaaagtgag actctgtctc taaaaaaaaa aaaaaaattt ctcagatgtg actcagtga 1440
ggattttgag atgggggagag tatcttggat tagccagggtc tgtgagaact cctgacgtct 1500

```

## 38

```

gaagcttgac tcccaagttt ccatagcaac aggaaaaaaa aaaatctatc caaatctgaa 1560
gattgcgggt tacagctatc gaacttcaca actaggcctc aattgttccg gttttttatt 1620
ttctttacaa tttcacttag tctgtacttc atcattttga cagcatcttc ctccctcctt 1680
taattaatgg aatcttctga attttccctg aatgtttaaa gatcatgaca tatgacttga 1740
tcttctggga gcaggaacaa tgactacttt ttctgggtgtg ttaacatgtc ggtgccgaat 1800
tcgatatcaa gcttatcgat accgtcgcac                                     1829

```

<210> 68  
 <211> 1688  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (912)  
 <223> n equals a,t,g, or c

```

<400> 68
acccaecgct ccgctcatgt ggacttatgc cagtctagag gcagaatcag aaggcttgggt 60
tgaacatatc gctttccctt ttccctctcc ctccgccctt cccagtacag tccatctttc 120
aatgttgacg cctgggttag aaggagagaa aaaggtggca ggaatttcca ggagatcccc 180
aagaatgctg ccttgtctgt ggacaaagat ggaccatgtg cccttcggaa ttagggatag 240
aaacaaatat tgtgtgctct taacgattaa gctgtgttat ggtgggtttt cagggtttta 300
ccttttttct ttaccccttt actctgcaag aatggggaaa gaatgcatac tgcgaaaatg 360
agtcttttaa attctgtctg cctactagtt ttaagtatat ggtatgttgt aaaatttcca 420
atgatgagag acagcacaat aaatgtacct tatctcctta ggctgaaggc cataactaca 480
tagtggagta atttaagaac tctcttgctt tcaccaaccc aaaagggttg tttttgatag 540
caactggcta atgaattttt aaaaagagaa gaaaaatact agttttcccc tcttttgga 600
aatagatttt aaatggctaa actactagcc ttaaaactac tagtctataa atcaactacc 660
acttttgtga atctgacagg ccacattttt atatggccct ttacagaatg gagtgtgttg 720
aacaggatac taacgccatg gagttgagct gggcctagcg atggaggagc actctaacac 780
aactttccct cagctattat gcaacagatc agggaaaaag atgggatgac agatgggggc 840
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agggtgccac tttctcaaga tgaaaactgt gactgaaaaa attaataata aatgtttctg 1080
agctgcctgt gttctccctg tgtgggtgag agaagggact agactcctaa gcctgcctca 1140
gatacaagag ggatcatttg ctccaatttt agagaacttg aaagcaaggc tttggacaaa 1200
attttgagac cctaataact ttaccttctt ccaaattacc caacatacgg taaacaacat 1260
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caaatgattt gaacttttat gcgactggga tttttttttt ccaaagctac aagcatggcc 1380
gcctgtggta tcgaggtgtt gcaacaata tctgtgttgc gcttccctgt ttaacctacc 1440
tcgttttgtt tgtttttgtt tcaactgttc tcacagcagt gttatctcca ggagacatat 1500
agagagctca accggcaatc tcaggtgcat ttaacatttt taaaacgaaa cagtagttga 1560
ccaaattttt cttcttaaaa aattggaagt ggggggaatc caatgacaaa aactaatgtg 1620
gcttggttct ggagaaaata attactgtaa atggaacaac aacaacaata aaacacacgt 1680
taaacatc                                     1688

```

<210> 69  
 <211> 565  
 <212> DNA

## 39

&lt;213&gt; Homo sapiens

&lt;400&gt; 69

```

tcattttgtg gacgaatatg atccaacaat agagagaaca aattaaaaga gttaaggact 60
ctgaagatgt acctatgggc ctagtaggaa ataaatgtga tttgccttct agaagcagtag 120
acacaaaaca ggctcaggac ttagcaagaa gttatggaat tccttttatt gaaacatcag 180
caaagacaag acaggggtgt gatgatgcct tctatacatt agttcgagaa attcgaaaac 240
ataaagaaaa gatgagcaaa gayggtaaaa agaagaaaaa gaagtcaaag acaaagtgtg 300
taattatgta aatacaattt gtactttttt ctttaaggcat actagtacaa gtggtaattt 360
ttgtacatta cactaaatta ttagcatttg ttttagcatt acctaatttt tttcctgctc 420
catgcagact gttagctttt accttaaatg cttattttta aatgacagtg gaagtttttt 480
tttcctctaa gtgccagtat tcccagagtt ttgggtttttg aactagcaat gcctgtggaa 540
aaagaaactg gaatacctaa gattt 565

```

&lt;210&gt; 70

&lt;211&gt; 675

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 70

```

ccagcatcag aagttctgat ggatgatgac cttcagaaaa gtgtggatat gatcatggat 60
atgttttgtc ctccaggaat aaaaattgat gcatatccgt gggtggaatg cttcatcaag 120
tcatacaatg tcacaaatgg aacagataat caaatttgct atcagatttt tgacaccaca 180
gtttgcagaag atgtaatcta atattgccat ccaatttagc atacataaaa tgttgccact 240
caccttcctt gtttgagctt cttttcctga cctgagtttt gtatcagcaa tgttgatgat 300
gttagcatgg gtatgggatt agaaaaatgtc cttaccttaa atctcttggc ttttactggg 360
tgcaaggtaa ataatggcta tggattttgt tttgctttct gttttgcttt tgtacaaaga 420
gacctgctta aacaagtact gctgagataa gtgtctgata aagctacagt gtactttaag 480
tagaaatggc aaagtttgctt tgttgggggtg ctgatactga tgattttagg ataaattcat 540
ttcttttaaac ttgtaataca tgggttttatt gcttgtttct cyccaggata gtagagattt 600
ctctattttca cctcaamcta ataaaagtgg tcagatttat aatgttaaaa aaaaaaaaaa 660
aaaaaaaaaa aaaaaa 675

```

&lt;210&gt; 71

&lt;211&gt; 270

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (247)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (260)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 71

```

ctgagatgcc acaagaagca gcacagtgat cagagtgaga acaagaactc agacttggtc 60
accttccccac cggaaagcgg tgcctcggga cagctcagca ccctgggtctc cgtggggcag 120

```

40

```

ctcgaggctc ccctagagcc cagccaagac ctctagctca gccgaagagg gtgggtcagct 180
gtcggaaactt ctgaccagtg ctgttgccca gccctccaga ggtgaggcca ctgagagaca 240
ggctttnggc accacttctn gggctggccg                                270

```

<210> 72  
 <211> 538  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (101)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (302)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (449)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (459)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (521)  
 <223> n equals a,t,g, or c

```

<400> 72
tatctcttgg cagcaggggt tgcaactgag aaacatgcaa ggtgggggat aattggatct 60
tgtgggtcag cctaccaaag tgctgggatt acaggcgtga ncaccatgct cggccagtca 120
gtatcatttt ttaaaaaatgt agaacctggt ttgatgactc taattaaatt gtctgccaat 180
tactgaagag ctactacata ctagwttctg ggcttttagtt ctaaagccca cagcaacctc 240
atgaataaat attattagcc ccaactgtata gatgagataa cagactagga gggagaagtt 300
anggaaactt gcttaatgcc tcctgttttag aaaatagctg aactggaatt cagccctgtc 360
ttccatttca cctgcctgt gtctcacgca cagaacaccc ggggatccgc tggttcccaa 420
agcactgatg agaaccctaa tttgtcaana ttcttgggnt ccagtaaatg gtggtccaga 480
atggtggggtg atctgatttc atattatctg ccaggtgaaa ngtttctgcc tggcaaaa 538

```

<210> 73  
 <211> 1071  
 <212> DNA  
 <213> Homo sapiens

<220>



## 41

<221> misc feature  
 <222> (1010)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1048)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1062)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1066)  
 <223> n equals a,t,g, or c

<400> 73  
 ggcaggagggc tgccgggggcg cgggctgctg cgggagaagg ggctccgagg agtccgcccgc 60  
 ggctcgctct gtcgccggcg cgggattggg gcgcgagggc catggggcgcg ctctcctaag 120  
 gcggagggtcg cgggcgggag gggaggaggc ccgagagagg ctgctgcgaa ggccgcgggc 180  
 ccgtgactgg gcgcgaggcg gccggcgggc gcggcggcac cagcaccacc atgtcgcgct 240  
 cagtgtgtgca gcccagtcag cagaagctgg cggagaagct caccatctc aacgaccggg 300  
 gcgtcgggcat gctcaccgc ctctacaaca tcaagaaggc atgtggagac cccaaggcaa 360  
 aaccatccta tcttatcgac aaaaacctgg aatctgtgt gaaattcata gtcagaaaat 420  
 tccctgctgt agaaaaccgc aacaacaatc aacagcttgc acaactacag aaagaaaaat 480  
 cagagattct gaaaaatctg gcattatatt acttcacatt tgtagatgtt atggaattta 540  
 aggaccatgt ttgtgaattg ctgaatacta ttgacgtttg ccaagtcttc ttgatatta 600  
 ctgtaaactt tgatttaaca agaactact tagattttaat tataacctat acaacactaa 660  
 tgatactgct gtctcgaatt gaagaaagga aggcaatcat tggattatac aactatgccc 720  
 atgaaatgac tcatggagca agtgacagag aataccacg ccttggccag atgattgtgg 780  
 attatgaaaa ccttttaaag aagatgatgg aagaatttgt accccatagc aagtctcttt 840  
 cagatgcact aatttctctt caaatggtat atcctcgaag gaatctttca gctgaccagt 900  
 ggagaaatgc ccagttattg agcctcatca gtgcacctag tacaatgctt aatccagcac 960  
 agtccgacac tatgccttgt gaatacctct ctttgggatg caatgggaan attggattat 1020  
 ctttggcttt atttgtgcca tggggatnct taaatacttg angctncagt a 1071

<210> 74  
 <211> 640  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (93)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature

&lt;222&gt; (96)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (619)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (624)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 74

```

gttgacagtga gccgagatca caccactgca ctccagcccg ggtgacagag caagactccg 60
tcataaatga ataaataaat aaataaataa tangtnacga tccattgtgg ctctctggaa 120
acatccatgt tcacagctgg ggtctgggtca gtctgcatag tggagcacac tgctaggatg 180
catccttagc aagtgaaaaa agtgaggctc agaactgttt gtagagtata gccttttatc 240
taaggaaggc agatgaagac tggcttatga taaagggtgct aacccccaga ctagtataaa 300
tgggggttccc tgtggagtag ggaaggggca gtgttataag ttggatttct ggccatatct 360
gctatagtac tgatcatgga actctagggg aggaagatg ttttccttct acccatctta 420
tgttcattgg ctggggctcc tggaacagaa gacagatttc caaagagaaa ggcacacmaa 480
tttatgtaat ataagtttgc catgacmtgg gagcctttat aaggaatgac cccaaggaaw 540
tggttaaacc tgagtggttt tgtgtaaggc tttaatgagc aatgaaaagc tatgggggacc 600
tatgatagga ggatgtaanc taanccaatg acctggggga 640

```

&lt;210&gt; 75

&lt;211&gt; 507

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 75

```

ggagcttcaa catatgaatt ttcagggtta tcattcagtc caaagtactt aakatgatgc 60
ttttccgttt ccacatagac aatcacataa tctgtaaata atgactctta cttttccact 120
ttagtcgtta gggtatacct atatatatat wwwmwgtgct tactggacta atttcaacct 180
ccagcacacc accaatgaat agcagtaata ccagcataat tgtctgcagt tctgctgaga 240
tacgtgctct attttattgg cttggctgta gggttttatt ttattttttg aagaggctaa 300
tctcttacag gaaagggttc tttttatata cagtttttac atgatgaatg atttcccagt 360
atttcataat tcatgaggct gaattcctct tgaatttatt aaatgcttcc tgtgcatcct 420
ctgtgatgat catgtttatt tactgctaga actcaagtac ctagaactgt tcctggccaa 480
tgatgggtatg taataaatac ttcaatg 507

```

&lt;210&gt; 76

&lt;211&gt; 1390

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 76

```

ggcacgaggg agtctgatgg ggagaagaag tacccatgcc ctgaatgtgg gagcttcttc 60
cgctctaagt cctacttgaa caaacacatc cagaagggtgc atgtccgggc tctcgggggc 120
cccctggggg acctggggcc tgcccttggc tcacctttct ctctcagca gaacatgtct 180

```

## 43

```

ctcctcgagt cctttgggtt tcagattggt cagtcggcat ttgcgtcatc tttagtagat 240
cctgagggtt accagcagcc catggggcct gaagggaat gaggcagctg ctgtgtcccc 300
acggaaacaa ccatctgggg actgctggga aatgctgtga atgcggaggg aagtgatgtt 360
tgggttctgt agctgagaga tttttattca tttttaactg cccccaacc ccaactccaac 420
tccttctcca ccacccattc tccaatggt ctttagaaat agattttcat ctgatattct 480
gcagaaatat caatgagact tggatatgga caggggcaga aaacactaca taggcctcca 540
aggcaaaacc agtcccagtt tctttaatgg gaagaagctg gaattcctgg tgctcaattc 600
ttagtgaccc caatcctata cccaaatcta tgatattctg ggacctcagt gatttttggtc 660
ccctcccaact tctctagttc gtcatcctcc cttcccatat ccttcaaaag aaccacacta 720
gggtctccac ctacttatac aatgcggatg cccaactgtt ttaaggaag ccagaagcat 780
cccatggacc atgggggtgag tgtcctccaa gagccccctg agctcagccc tctgcctgga 840
gggtctccaga cctttctgag ccctgcttgg aggcgagcat ttctactgct aggacaagct 900
cagctgttga ggacaccccc accccaaatt tcagttctta cgtgatttta accattcaac 960
atgctgttgg gttttaattc tctaattatt attattattg ttattatttt ttaggaccag 1020
ttgtagtgaa ttgctactga aagctatccc aggtgataca gagctctttg taaaccgcag 1080
tcacacatta gggtagtat taaactttgt ttagatgtac cataattaac ttggctagtt 1140
gattgtttga agtctatgga agaaatagtt ttatgcaaaa ttttaaaaaa tgccagtctg 1200
gtcagggaag taggggggtt caatgctgtt gggaaccagg aaggtgggac agccggcagg 1260
tagggacatt gtgtacctca gttgtgtcac atgtgagcaa gccaggttg accttgtgat 1320
gtgaattgat ctgatcagac tgtattaaaa atgttagtac attaaaaaaa aaaaaaaaaa 1380
aaaaaaaaaa 1390

```

<210> 77

<211> 782

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (29)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (34)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (738)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (748)

<223> n equals a,t,g, or c

<400> 77

```

gggcacgagc tcgtgccgaa ttcggccang aggnacctga gcagtctaac tactccagtt 60
agacctaagg gcacaaatgc agaattcatg acctttagt tgtggcaggg tctaggaagt 120
cctctctccc caagtagaaa atattctctt gccattcctg aaattccaca ttcataataat 180

```

## 44

```

ggctgtgcaa tacatgcttc tcaataagaa aattaactgc atgtttactg tgtgctgac 240
acatcagatt tttatgttta aaaaaatctc attatggatt gagtccagcc cagctctaag 300
agaaaaagaa ggcccatatg ggagacttca stctcattat tattgccttt atccagcagt 360
gcttatgaag cccctaccc tgtccattc cagaaacat aagactcagg cagttcttga 420
ttctggaggc ctgcctggta agataagata gtataatttg gaactgagaa cataccagaa 480
acagcagaac gagggccaga gcagaaaaat gaaaataagt ggagacactt atggatacat 540
tggtgcaaaa aaagccacgg agcccatact gggcttgata tgactttgag gggacagcag 600
attaatactt aatgagggtt aaacctgacc agtctttcta cagtgcagag ccacactgca 660
tgaatgggga gaaccaatga atccattgtc ctctgcctat tttctgtgc acagtcacat 720
cccctcctta agaatctncc ccttccancc tttacattaa ccaagggaca ctgaatcttt 780
ca 782

```

&lt;210&gt; 78

&lt;211&gt; 278

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (8)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (27)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 78

```

cttctcgnctg cccgtgcaaa ggctccnctg cagaagacat cctytggcag cctgctcttc 60
tgctgctcct tttgctgctg tcccatgtgc tcttgagaat gagaaccctg cctttgcaac 120
aaaccatgcc ccggtaaatg caaaaccaca tgctctgtgc cccgagagaa aacctctaac 180
cagcaaggaa aatgtattga tgcattcctc catthttggca cctgraagag agtcttggrg 240
aactgcagga gagggggaaa actggaaaaa aaaaaaag 278

```

&lt;210&gt; 79

&lt;211&gt; 828

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 79

```

gccaatcaat gagcagtata gagaatttct ggaaggaggaga cacaagaagc tgttagaaaag 60
ggcggcttcc aggggaagttc tagggagtct gggatgaatg agaaacttat cctaacaact 120
tttgggctct ctgaattttt tttagtatct gcaagtattg tacttggtca aatatgttta 180
aggctgcagg ctgtattcta aactccttga aagtgagaa caggtttcac tcatatttcc 240
atcttttcaa cccctagatc agtgacttcc cagggaagta gtacctgcat ttgggggtga 300
cctttgggtt tcccctgtac tggcttgcc tggcctggct ggacctgg stggctgggt 360
ggctgtgacc tagcccttc tttctcttg ctctctgtc aaatgagagt gttgggtctga 420
acgatctcta aagcctggaa gaggagcaga tctctgtgc tcagcccca ctctgtgtca 480
gggaggcctg gcaaccacag tgttctttct cctgtttatt tgttcttggga tcttctgaa 540
gccatttcac caccagcctt catcttctct gccagcccca tggagactca agcttttcc 600
agcctatgtc aggggaaggag aaccagagac agcaacctcg ggtgtgaagg gagtcagctc 660

```

## 45

```
tgaacccagg actatggcct tctgccactg cctgctttcc tcttgctgct ggggcctagg 720
tcttcttgct gctgcttcct tttccgctaa tcaagagtc agggaggtgg gaacagcctc 780
aacaagact ttgaagatga gcggggagga tcgcttgagc ccaggagc 828
```

<210> 80  
 <211> 342  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (198)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (215)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (319)  
 <223> n equals a,t,g, or c

```
<400> 80
caagttggga agaactgata tcttacggat actgttaaag agaactaaat atggcctgag 60
aaggactccr tatttctata tttgartcct tgtgggtgaa ccaaaccta gcttaatagg 120
tagacaatat tgaaaaccta acctagaagt atgcacctgt aacaatagct aggtcttggc 180
caatgcctgt ggccatannt cagccattca tacantgctg agtgttcaa gtctgttcaa 240
ataagggaaa caacgaggtg taaccaatcc agctgttctt taccttactt ccaaattctg 300
tacgtcattt cccattttnt gtctataaac cttcttccac ca 342
```

<210> 81  
 <211> 537  
 <212> DNA  
 <213> Homo sapiens

```
<400> 81
ggctttacgg ctgcgagaag acgacagaag ggggggggacc atgttgcttc cgaacatcct 60
gctcaccggg acaccagggg ttggaaaaac cacactaggc aaagaacttg cgtcaaaatc 120
aggactgaaa tacattaatg tgggtgattt agctcgagaa gagcaattgt atgatggcta 180
tgatgaagag tatgactgtc ccattttaga tgaagacaga gtagttgatg agttagataa 240
ccaaatgaga gaaggtggag ttattgttga ttaccatggg tgtgatttct tccctgaacg 300
ctggtttcat atagtttttg tgctgagaac agataccaat gtattgtacg aaagacttga 360
aacaaggggt tataatgaga agaaactaac agacaatatt cagtgtgaga tttttcaagt 420
tctttatgaa gaagccacag catcctacaa ggaagaaatc gtgcatcagc tgcccagtaa 480
taaaccagaa gagctagaaa ataatgtaga tcagatcttg aaatggattg agcagtt 537
```

<210> 82  
 <211> 292  
 <212> DNA

<213> Homo sapiens

<400> 82

```
tggacagaaa attcaatcct ttattttttt ctctgtaaat gcacgggcta tgagatagca 60
acaaaaaatg catagttaat ggtcatagac ttatttccaa aacataattg gaaaatagaa 120
wctgagccat tgccaaatgg taaagaaatg aaaagttttc acagtgacta ctgaatatac 180
caagagcttt tggcagtact gctggctttc tgggtgatta attaggtaaa cttggaatat 240
tcccagtaaa agtttgagaa tgcataaaat tataccattt tgaaaaatat aa 292
```

<210> 83

<211> 352

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (291)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (345)

<223> n equals a,t,g, or c

<400> 83

```
ggcagagtk aaacttgctg ttttgttcct gtgtcttgct tttggttggg atttcagtaa 60
gttttttgta ttctcaaatt ttatctaaat ggataaacta ttaacataga acataaaccc 120
caattctcca ttctattttt ctcttaggca tgaatcatac aaaactcaat atagagcaat 180
gtttgtaatg aattgttcta ttaacaaaga ggaggttcta agatrtaaa cctcagagga 240
acaggaagga aaaggcgggt ccataaggaa gatgaggtct taaccgggga ngatgctgct 300
tgaggaggggc cagagacagt tgtgggagga aatcttttca ccccnttcat gt 352
```

<210> 84

<211> 404

<212> DNA

<213> Homo sapiens

<400> 84

```
cccccccct tttttttttt tttttttttt tttttttttt tgcgattgct ttaaagaaag 60
ctttatttac tacatacatc ctaagaatgt actgtaaatg gagcaagatc taaataaaaag 120
cttttcaaat ataaagcagc taaagttaac taaaccacta gcaatgtttg aaaacagAAC 180
tctaaaactt tttttttaca tttatatagt ttgttcttaa cactaaaaaa aaaaaagtTC 240
acatttcaag ttataaactt acctcagtag tgtacatgaa atgggttttga aacaatagga 300
acagataagt cccagatagg rggctcactg atacttaatt ggccatgtca ccaatgtttg 360
tttttaaggg rgtttggtgg ttgccatggt tatcattttt tttt 404
```

<210> 85

<211> 1555

<212> DNA

<213> Homo sapiens

47

&lt;400&gt; 85

```

ggcacaggac agtctcatga ttataactgg tccttcaagt atacagggaa tataataaag 60
ggtgttataa acatgggttc ctacaactat cttggatttg cacggaatac tggatcatgt 120
caagaagcag ccgccaaagt ccttgaggag tatggagctg gagtgtgcag tactcggcag 180
gaaattggaa acctgggaca agcatgaaga actagaggag cttgtagcaa gggtcttagg 240
agtagaagct gctatggcgt atggcatggg atttgcaacg aattcaatga acattcctgc 300
tcttgttggc aaagggttgcc tgattctgag tgatgaactg aaccatgcat cactggttct 360
gggagccaga ctgtcaggag cmaccattag aatcttcaaa cacaacaata tgcaaagcct 420
agagaagcta ttgaaagatg ccattgttta tggtcagcct cggacacgaa ggccctggaa 480
gaaaattctc atccttgtgg aaggaatata tagcatggag ggatctattg ttcgtcttcc 540
tgaagtgatt gccctcaaga agaaatacaa ggcatacttg tatctggatg aggctcacag 600
cattggcgcc ctgggccccca caggccgggg tgtgggtggag tactttggcc tggatcccga 660
ggatgtggat gttatgatgg gaacgttcac aaagagtttt ggtgcttctg gaggatata 720
tggaggcaag aaggagctga tagactacct gcgaacacat tctcatagtg cagtgtatgc 780
cacgtcattg tcacctcctg tagtgaggca gatcatcacc tccatgaagt gcatcatggg 840
gcaggatggc accagccttg gtaaagagtg tgtacaacag ttagctgaaa acaccaggta 900
tttcaggaga cgcctgaaaag agatgggctt catcatctat ggaaatgaag actctccagt 960
agtgcctttg atgctctaca tgctgcca aattggcgcc tttggacggg agatgctgaa 1020
gcggaacatc ggtgtcgttg tggttggatt tcctgccacc ccaattattg agtcagagc 1080
caggttttgc ctgtcagcag ctcatacc aaataactt gatactgctt taaaggagat 1140
agatgaagtt ggggacctat tgcagctgaa gtattccgt catcggttgg tacctctact 1200
ggacaggccc tttgacgaga cgacgtatga agaaacagaa gactgagcct ttttgggtgct 1260
ccctcagagg aactctccct caccaggac racctgtggc ctttgtgagc cagttccagg 1320
aaccacactt ctgtggccat ctacgtgaa agacattgcc tcagctactg aagggtggcca 1380
cctccactct aaatgacatt ttgtaaatag taaaaaactg cttctaatec ttcttttgct 1440
aaatctcacc tttaaaaaacg aagggtgact actttgcttt ttcagtccat taaaaaaaca 1500
ttttattttg caaccattct acttgtaaaa ccacgccgag ccctatgcag tctca 1555

```

&lt;210&gt; 86

&lt;211&gt; 455

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (430)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 86

```

ggcacgagcc agagccgact gcaaatcact gaactgagct ggcagctgct taggggtttg 60
catgatcaag gcgattttta taacctagaa gggcctggac tgtagaagca gattccagct 120
gaggccagg cactgccttg ctgtggtgag cacggcggt ctgstcttcc ccgccgagct 180
ttctcatcag tgaagtggg tagtgacagc atgcgagggc acggagctgt cagcaggctc 240
cagagaccat ggccataaag cactgacact gacacggccc cagcaagccc ttkgggaagg 300
gcagccacca cckttgctgc tgytgctact tactgttgct gttgatttaa ggcaaktacat 360
actcaggyt catagcttgt aaaamaaagg aaaaatgaaa agtcaccatc atcccagcaa 420
aatgtaaggn tcccctgctg ccagatttg aatgt 455

```

&lt;210&gt; 87

&lt;211&gt; 675

&lt;212&gt; DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (427)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (528)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (564)

<223> n equals a,t,g, or c

<400> 87

```

ggcacgaggt cgggctcggg ggaggatcca gagacggagt ctgggcccgc tgtggagcgc 60
tgcgggggtcc tcagtaagtg gacaaactac attcatgggt ggcaggatcg ttgggtagtt 120
ttgaaaaata atgctctgag ttactacaaa tctgaagatg aaacagagta tggctgcaga 180
ggatccatct gtcttagcaa ggctgtcatc acacctcacg attttkatga atgtcgattt 240
gatattagt taaatgatag tgtttggtat ctctgtgctc aggatccaga tcatagacag 300
caatggatag atgccattga acagcacaag actgaatctg grtatggatc tgaatccagc 360
ttgcgtcgac atgggtcaat ggtgtccctg gtgtctggag caagtggkta ctctgaaaca 420
tccaccnctt cattcaagaa aggccacagt ttacgtgaga agttggctga aatggaaaca 480
tttagagaca tcttatgtag acaagttgac acgctacaga agtacttnga tgcctgtgct 540
gatgctgtct ctaaggatga actncaaagg gataaagtgg tagaagatga tgaagatgac 600
tttctacaa cgcgttctga tggtgacttc ttgcatagca ccaacgggaa taaagaaaag 660
ttatttccac atgtg 675

```

<210> 88

<211> 493

<212> DNA

<213> Homo sapiens

<400> 88

```

gtcgccctag gctgggactc tagtaggtct tcggctcagt tttggctgca gcgcccgcgt 60
agatcgcttc ggccgsgttc tacgcccggc tcaactatga gcckgtgcgc ccaggcggcg 120
gaagtggcgg ccacagtgcc aggtgccggc gtcgggaacg tggggctgcg gccgcccag 180
gtgcccgcgt agcgtccttc ttcccgcgcg cggtgccgaa ccccttcgtg cagcagacgc 240
agatcggtct cgcgaggcgg gtccagattg tccttcttgg gattatcttg cttccaattc 300
gtgtcttatt ggttgcggtta atttattact tgcattggcca ttgctgcatt tcaacagtat 360
gctgtcctga aaagctgacc caccataata ctggttgagg gaggtgaagaa atattttgtc 420
caaaatatta ggacataata ttaaattaag atatactaaa tcaatataag aagagttcat 480
catagtttag tca 493

```

<210> 89

<211> 416

<212> DNA

<213> Homo sapiens



&lt;400&gt; 89

```

gtgggggatgg tgtcgcatag cagccgctgc cgctttggct tgctcgggac catttggtcg 60
gaccagaggt ccgcgtggaa ccgcgatagg gatctgtcag ggcccgcggc cgggtccagc 120
ttggtgggtt cggtagttag aggcctccgc tggttgccag gcttggtcta gaggtggagc 180
acagtgaag aattcaagat gccacctawt ataaactgga aagaaataat gaaagttgac 240
ccagatgacc tgccccgtca agaagaactg gcagataatt tttgatttcc ttatccaagg 300
tggaagtaar tgagctaaaa agtgaaaagc aagaaaatgt gatacacctt ttcagaatta 360
ctcagtcac taatgaagat gaaagctcaa gaagtggagc tggctttgga agaagt 416

```

&lt;210&gt; 90

&lt;211&gt; 1467

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 90

```

ggcacgagtt catcttcac tttcagctt gctccaaatg gtgcaaatg cattccagta 60
cgagaccgtg gcttcctggt gcagacaatt gagtttgctg aacagcggat ccctgtatta 120
aatgaatatt gtgtggtttg tgatgagcca catgtgtttc aaaatggccc tatgcttagg 180
cctaccgtat gtgaacggga gctgtgtgtg tttgcttttc aaaccctggg agtaatgaat 240
gaagctgctg atgaaatagc aactggagct caggtggtag atctactagt atccatgtgt 300
aggtctgctg tggaatctcc tagaaaagtt gtgattttcg agccatatcc ttctgtggtg 360
gatcctaata atcctcagat gttggccttc aaccccagga aaaagaacta tgatcgagta 420
atgaaagcac tggatagcat aacttctatc agagaaatga cacaagcacc atatctggaa 480
atcaagaagc aaatggataa acaggacccc cttgtctatc cttactgca atgggttata 540
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tccatcctga ggaatggtct ggttggtgct tctaatacac gattgcagct ccatggtgca 780
atgtatggaa gtggaatcta tcttagtcca atgtcaagca tatcatttgg ttactcaggg 840
atgaacaaga aacagaaggt gtcagccaag gacgagccag cttcaagcag taaaagcagc 900
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ttattataaa caaaattaac cttttgaata ctgatttttt ttcttagtat ttctaagtat 1320
ctcattaaat acctaaaatg gtataagatt tatcaattgt agggttatgg aatctagtaa 1380
taaaatttca acagcactta aactgaagtt tgggttgctc atacaataaa cagattgaaa 1440
aaacaaaaaa aaaaaaaaaa aaaaaaa 1467

```

&lt;210&gt; 91

&lt;211&gt; 1793

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 91

```

ccacgcgtcc gatttgtccc tattgttcta tttttaata aatatacaat cattgttttg 60
cattgaaatg catatttgta cattttattt gataatatta ttttgggaaa ttgtaatctg 120
ttgttttgtt tgtttgtaa gggaagcacg aagaagaatt taaaaatgtg aataaaattg 180

```

```

ttaaagatta ccaatagttt cttttctgga cttgaaatag ttacgtttct aaatatgaga 240
aaaataactt tgcctaaaat ttcagtataa tgaccagggtc ttctctccat tttagagaag 300
cagtccaatg tggacagat aagacggcag cgatccagtg aggtcaattc cccacagagg 360
aaagctatgc atacctaact taatggaagg taaacttctc ttcaattaat gatgtcctcc 420
ttttctcaag gtgtccaaag acaggagggtg gtctgtaaaa ggttggaatga caactccatt 480
gtccagaaca attactgtga tcctgacagt aagccacctg aaaatcaaag agcctgcaac 540
actgagccct gcccacctga gtggttcatt ggggattggt tggaaatgcag caagacttgt 600
gatggtggga tgcgcacaag ggcagtgtct tgcacagga agatcggacc ttctgaggag 660
gagacgttg actacagtgg ttgtttaaca caccggcctg tcgaaaaaga gccctgcaac 720
aaccagtcag gtccaccaca gtgggtggct ttggactggt ctgagtgtac tccaaaatgt 780
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tccaaatagt ccatttcatt aggaactttt ttgtttgaat gaatgtcaca taggtatcct 1500
cagtaacaca gaacgaaatt acctttgtat tattgtgatt agttgttgct tattatttta 1560
tactcagtaa taatgtggta cactgttaat ttttttgctt ttgtaaatta tattctaatt 1620
tattgccatg tttcctaaca cttgtcctac attcattctc ctgcttgtaa tgaaaatgaa 1680
aaaatcattg taacacttga tggagtgaat ttccacgcca ggcacagaat ttttttgaca 1740
tagataatth agtaaaaataa aaattcagct tataataaaa aaaaaaaaaa aaa 1793

```

&lt;210&gt; 92

&lt;211&gt; 538

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (24)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (53)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 92

```

gccaaggat tccggcacga gganttkttg ttggttgggg gccttttggc sgntgacgga 60
gactgcccag gtgtggtcac catgttcctc tccgcgggtc tctttgcca gagcaagtca 120
aaaaacattc tgggtgagaat ggtgagcgaa gctgggacag gtttctgctt caacaccaag 180
agaaaccgac tgcgggaaaa actgactctt ttgcattatg atccagttgt gaaacaaaga 240
gtcctcttcg tggaaaaagaa aaaaatacgc tccctttaa cggtggattg aaaatgactt 300
tgatttataa agagaagact gagggcgggg atactgattc agaaatcctg tagcgtgtaa 360
taaaagaaga ggaaatggca tggaaatcact gcctcctgtg atttgaaggc cattgtgaag 420

```

## 51

gaaaacaatg cagtgaaaga aagttcttca tattaggaca gatatcattg catcacattt 480  
 atttatcttt ctgggtattt ttatagccct taataaaaaa tattaaaatw gwaaaaaa 538

<210> 93  
 <211> 483  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (444)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (483)  
 <223> n equals a,t,g, or c

<400> 93  
 gggaatctat cataactagt ctagagattt ctcaccaagg gaaattttcc ttatctaaaa 60  
 gaggaacttc aggtctcaac cctgccagtc acaccaatt aatgtccttc aaaaaataa 120  
 acagcatatg ttccctttca atttgagttc agtgagctca cagcaaaatt taccttttaa 180  
 ttttcttcag caaatccaag acgaatatac aaaggatgag attagataaa gatttcagtt 240  
 tcccgtatgc caccgctggc cgccaatttt ccaaaaaagc ctggctctc ttttctgtt 300  
 cctccatcca agccccaaa gatctctaac cagaawtaaa caggaagact cagtgattta 360  
 caaaagacat tttagtttta caggtacaga aaattctacc cagcattaca gaaattctta 420  
 gacttcttaa aattcccggg tttnccttgg tatttaacat ttggataagg gagccatggg 480  
 ttn 483

<210> 94  
 <211> 719  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (1)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (619)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (633)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature

&lt;222&gt; (643)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (646)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 94

```

ngggaattgc tgagatgaca gtgtccacaca cagcttcaaa taaaatccat ggaaagatgt 60
tgcatttgtg gaataagtgc ttacttgaaa agcatgttct tcttttattt tcttactgtt 120
aagaattttt atttgttagga tgtttgtttt aatttaattt ttttaaggga tgggggcat 180
catgtggaaa ccagaaaatg gggaaagtgt gaactatcca gacaaagatt cattttgtgt 240
ctatatattgt ttttaattgg cctcatttca aatgtattaa acagttccat acctggattg 300
ggtgtttgtg atggttacca aaaaacaaac aaaaaaagaa agaaaaagga aaaaaaaaaa 360
gaaaataatt gtgacatgct tttatcacta ctttattttt caaataacat gtaaattattg 420
taatccattg gattttgttt tgctaacctg ttaataaaaa tatgggacca ttatcctttt 480
aacaaggcta gaatgtcatt tttttctttt tcaacatata cctgatattt tgtggccgca 540
cattttgggt gcattattat aattckgttg actgtaatga catagaatta cacattttkt 600
gktggttaat tatacagang acattttttt canagcttga ganaanaaaa taaatagcaa 660
aatgataacc tattgactcc agtaatcagt gtttcccaat acttcataag aaataggga 719

```

&lt;210&gt; 95

&lt;211&gt; 613

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 95

```

tattcagcta ctatacagaa aaaggatgaa caaattaatt tatttctaatt tgagccagtt 60
agacataatg catataacgt gatatttgggt tcatgaaaga gttgttttca tgtggttatt 120
gtaggagta tatataattg tggaaggggt atgggaagag ttgtgtatag ttagttgtta 180
tctctacaag tttgaaagtt ttcccatcaa acattatcaa tataccaatg ttttaaaaaat 240
tgagtgaggg ttattatttg tatttgatga aagaaaatcc aaataaagcc cacctagaaa 300
tagatatttt attatatatg tgctatagat atacctatat agtacaaata gacatgtgtg 360
atgcataatat acaatgttat atatgtgtat atgtctgtat acacactgag tctgtaatat 420
gtatacacta aatttgtgky amgctaacak cttcagggtc tgcactgtga actccccgk 480
agataagtaa gtccacttta gaataaagag ttcttttgag acttcagtta ctaacgtgct 540
ttaagaggta tctactttat aactgaattc tatgtcgttc atacgtagag ttacagtaag 600
ggtctagtat gtc 613

```

&lt;210&gt; 96

&lt;211&gt; 816

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 96

```

gggaaaggag ggtcaggcga gtccacgagg aggttcgagt gaagatcaaa gacttgaatg 60
aacacattgt ttgctgccta tgcgccggct acttcgtgga tgccaccacc atcacagagt 120
gtcttcatac tttctgcaag agttgtattg tgaagtacct ccaaactagc aagtactgcc 180
ccatgtgcaa cattaagatc cagcagacac agccactgct caacctcaaa ctggaccggg 240
tcatgcagga catcgtgtat aagctgggtgc ctggcttgca agacagtga gagaaacgga 300

```

## 53

```

ttcgggaatt ctaccagtcc cgagggtttgg accgggtcac ccagcccact ggggaagagc 360
cagcactgag caacctcggc ctcccccttca gcagctttga ccactctaaa gcccactact 420
atcgctatga tgagcagttg aacctgtgcc tggagcggct gagttctggc aaagacaaga 480
ataaaagcgt cctgcagaac aagtatgtcc gatgttctgt tagagctgag gtacgccatc 540
tccggagggt cctgtgtcac cgcttgatgc taaaccctca gcatgtgcag ctcttttttg 600
acaatgaagt tctccctgat cacatgacaa tgaagcagat atggctctcc cgctggttcg 660
gcaagccatc cccctttgctt ttacaataca gtgtgaaaga gaagaggagg ttagccaagc 720
ccccaccca tcccactccc cttccctcmc cagatattta tgtgaaatga actgcagctt 780
tattttttga aataaaaaact tttaaaaagc aaaaaa 816

```

&lt;210&gt; 97

&lt;211&gt; 577

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (38)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (575)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 97

```

cagaagccaa aaaggtctta aaattggaaa tagatgtntt tattgtactt cagccaacag 60
caagccaggg gaaggaacat acataaatat gacagggtcat atatgaaatt tggctctcct 120
cctatcaaag tagcctagga gcttggagga agcctaatta actaaaacag gaaaaaagca 180
tactcatctg atgtaaaaac tcatcagctg taaattacca acattaaacc agaagtcatt 240
accagttaaa atgtgtggtt ttcattctat tcttaaatag gagagggtggr cagtagtgta 300
agtaacattg ctttaaagrc ataaagcttk tcctggtaaa catggtctaa atgagaaatg 360
cctccatctt ttcaggtaga accagatttc aggcatagct cagctacatc tgtatttgaa 420
atacaataaaa aatatttctt atgtctctgt attctctttt aaaaagaact gctgactggc 480
tcctgtctct tcagtaaacac tgattttttt ttaaagaagt gatatgttgg actctgttgg 540
agaagaatga gcactagtat tcagccacaa gtgcnat 577

```

&lt;210&gt; 98

&lt;211&gt; 484

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (456)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (476)

&lt;223&gt; n equals a,t,g, or c

54

&lt;400&gt; 98

```

cttgca gtc acttgctgaa gaagttgtgt catttctctg gaagaatttc caaaattctg 60
gattttttt tttttttgga gtatttcac agctgaaaag tgattctyac tttgagtttt 120
cttcctatat ttgtatagt agttcccttt tccttcctct ttatccctcc tgttttactt 180
tatacctctc tattccttgc tcaaattatt gcaaaagcct ctatagaaag tcctctgtga 240
tctgactcct gcagactctt ccagattttt ctgccaagg cctttactga gctcaggact 300
ccagctaaat caaratackc atgttctcac ccagagtgc aaaatcctgc agatagggtt 360
aagacctagt gggmtcagag cagtagctac tgggaagtta aaaggaagg gttagaaaat 420
gaatgggaca aaggcacact tctgatggag atgaancact tgaaagtgc tggtgncttt 480
ggag

```

&lt;210&gt; 99

&lt;211&gt; 441

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (328)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (331)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (332)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 99

```

aattcg gca agggaaaaag gctgagcgga gagccgtgct gcctggcccc tcctcaccgc 60
ccttccccgc acctcttggc tgtaccggga gcctctgaag caccggaaat gaagggtttt 120
ccaggcctgg ctcttcaacts catccttcag gggaactttg aagccatgga gacatctggc 180
tttgaggcca tggcgattcc cctgccactc tccttgctgg gataaagcca gggcgtggca 240
tcctgggatg atgttccctg ctgctgagtg tgcacacaac ctgagctcat cctgtgtacg 300
tcagctacac atgctcgcat ctaatttncc nnaacaacct agccagtact attgcttctc 360
ctcctcttac agatggggag atgatgacat atagagggtta acttatcaga gaccacacaa 420
aaaaaaaaa aaaaaactcg a

```

&lt;210&gt; 100

&lt;211&gt; 524

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (510)

&lt;223&gt; n equals a,t,g, or c

55

&lt;400&gt; 100

```

aaagaaaacg aaaaagaaaag cccaaggcaa agaaggggga aggaaaacaa acttcgccac 60
tctytcttct ccttcctaac cctttgtyta gagcaccaca ccgctcacia actctttcca 120
aatgctcagt tggctcccaa agttggagcc tggcatgggc akggagccca caaaactcta 180
accaaactgg akgtctggcat gggagaartg cttctggttc actcttecta cctctccct 240
cctaaccctc tccttgccctg acagggagcc cctgtggcct ggactctagg ggatgccgcc 300
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tgccacgttg aggggtccaac ctccaaggga caggcactgc cccaccaacg gcaaatacaa 480
aattctttca aaaaaaaaaa actgaaaacn caacccaaaa aagc 524

```

&lt;210&gt; 101

&lt;211&gt; 614

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (355)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 101

```

ggagaagggt tctctctcat ctccttctcc agcaaccttg gccatggacc agccggctgg 60
cctgcagggt gactacgtct tccgggggtgt ggagcatgcc gtgcgggtga tggtttctgg 120
gcagggtgct gagctggarg tggaggaccg gatgacggct gaccagtggc ggggagagtt 180
cgatgctggc ttcatggaag atttgactca caagacaggg aacttcaaac agttcaacat 240
cttctgtcat atgctggagt cagccctcac tcagagtagt gagtcagtca ccttggaact 300
gctgacctac acagacctgg agtccctgcy gaaccgaaga tggggggccg ccagntcctt 360
ggccccagcgc tcggccccagc tcaactccaa gcgctacctg atcctcatct actccgtgga 420
gtttgacagg attcactacc cgctgcccc cccgtaccag ggcaagccag accccgtggg 480
tctgcagggc atcatccggt cactgaagga ggaactgggc cgctgcccc gtccctgccc 540
tggccccgct cctcctgctg cccctggggg tctcaggtgt gtgaggccct gaccctgccc 600
tctccccagg cagt 614

```

&lt;210&gt; 102

&lt;211&gt; 544

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (5)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

<221> misc feature  
 <222> (6)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (10)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (12)  
 <223> n equals a,t,g, or c

<400> 102  
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 cgctctagaa ctagtggatc ccccgggctg caggaattcg gcacgagaga aaaattat 120  
 gtatataact ttaaaaggag tagaagggct ttttgcagag ttattacgtt tgaagtatac 180  
 tttatttctt gaaaaaatta cagatttttt gtaaataatg atgtaattca actctcaaaa 240  
 tatttccctac tgtttcttta ttccagttgt attcacatgt gaaagcatgt gatcagttat 300  
 tgctgcatta aaacatgag tcttttttat taggtggcca ttatttatga tcttttctat 360  
 gaaagagtaa ggacattaaa atgtaagatg catgatgaaa aattaagtga agaggctctt 420  
 tatggttaat ttatattgaa taatgcatta ggtaggtgtt cagagtaata ttttgcgttg 480  
 tgagaacatt ttttaatttta tttaaaatta aatgaaaata aattagtata ttattgtact 540  
 aatt 544

<210> 103  
 <211> 1887  
 <212> DNA  
 <213> Homo sapiens

<400> 103  
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 gtgacgtgca ggggaccaga ggctctgcac tgctcctagg acagctcatc tgtaatcaga 120  
 aaaaaataaa ataaaaataca gaacgctgac tcctcctgta gacagatcgg ggaccttagc 180  
 actttaatcc ctcccttctg agcgctcggt gtgcactttt agactatagc tgtttcattg 240  
 acgtgtcact ctccatccag tgctcctgat gtggccttta gagacttagc agaaaattcg 300  
 acacaagcag gaacttgatt ttttaagaaa aaatattaca ttttgaggac attttgacaa 360  
 gtaggggaag agagggcttc tggtgttttg ttttgttttg ttaactaaac ctgaagtatt 420  
 aattccacaa agacactgtc cctcaggacc actcaggtag agctctgcca gggacagagt 480  
 ctgctagtgg gaggtctcag gtggggcggt gtgttctgtg ccatgaggca ggcacaggtc 540  
 cagatggatg tcgtcaccac ctccctcagc tctcatcacc tggctcgtag ccaggccccac 600  
 ctcttccag caagggacgc caaagaactg cagtttttat tctgagtctt aatttaactt 660  
 ttcattcatct tttcctat 720  
 tgcaagccag tatctcacia ggcattgatt tctgtggaat ttatttttat tcaaataacc 780  
 atatttatct ccaggctgtg gaatcgccac tttctttgtg aagacagtgt ctctccttgt 840  
 aatctcacac aggtacactg aggaggggac ggctccgtct tcacattgtg cacagatctg 900  
 aggatgggat tagcgastgt gggagactgc acatccggac ctgccccatgt ctcaaaacaa 960  
 acacatgtac agtggctctt tttccttctc aaacacttta ccccgagaagc aggtggctctg 1020  
 cccagggcat aaagaaggaa aattggccat ctttccacc tctaaattct gtaaaattat 1080  
 agacttgctc aaaagattcc tttttatcat cccacgctg tgtaagtgga aagggcattg 1140



57

```

tgttccgtgt gtgtccagtt tacagcgtct ctgcccccta gcgtgttttg tgacaatctc 1200
cctgggtgag gagtgggtgc acccagcccc gagggcagtg gttgctcggg gccttccgtg 1260
tgagttctag tgttccacttg atgccgggga atagaattag agaaaactct gacctgccgg 1320
gttccaggga ctgktggagg tggatggcag gtccgactcg accatgactt agttgtaagg 1380
gtgtgtcggc ttttycagtc tcatgtgaaa atcctcctgt ctctggcagc actgtctgca 1440
ctttcttggt tactgtttga agggacgagt accaagccac aagaacactt cttttggcca 1500
cagcataagc tgatggtatg taaggaaccg atgggccatt aaacatgaac tgaacggtta 1560
aaagcacagt ctatggaacg ctaatggagt cagccccctaa agctgtttgc tttttcaggc 1620
tttggtattac atgcttttaa tttgatttta gaatctggac actttctatg aatgtaattc 1680
ggctgagaaa catgttgctg agatgcaatc ctctgtgttc tctgtatgta aatctgtgta 1740
tacaccacac gttacaactg catgagcttc ctctcgca agaccagctg gaactgagca 1800
tgagacgctg tcaataacag acaaaggatt tgagatgttc tcaataaaaa gaaaatgttt 1860
cactaaaaaa aaaaaaaaaa aactcga 1887

```

```

<210> 104
<211> 253
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (226)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (228)
<223> n equals a,t,g, or c

```

```

<400> 104
agattttgaa cttaaattat attctatatg tgtatcttcc taggcaaaag ctgtaatttc 60
cagagagacc attaggaaca ggtagtatct atttctctcc attatttatt tctagaaact 120
cataaaatgg attgtatttt tctataagaa caaaatatta attaaggtat agatgactga 180
ccaagggstt aatcaataaa aatgactaac agcatctatc cataangnca cacaagcctt 240
atgttctcat ctt 253

```

```

<210> 105
<211> 705
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (671)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (688)
<223> n equals a,t,g, or c

```

<220>  
 <221> misc feature  
 <222> (698)  
 <223> n equals a,t,g, or c

<400> 105  
 cccaatctct agctagtgtt gcttatcaaa taaatgcatt ggccaacaat gtactccagt 60  
 tgctggatat ccaagcctct cagcttcgga gaatggagtc ttccatcaat catatctcac 120  
 agactgtgga tattcataag gagaaagtgg cacgaagaga gattggtatt ttgacaacaa 180  
 ataagaatac atcaagaact cacaaaataa tagcacctgc gaatatggag cgccctgtaa 240  
 gtatatctcg aaacctatcg attacacagt tctggatgat gtgggccatg gtgtcaagtg 300  
 gctaaaagcc aagcatggaa ataaccagcc tgcaagaact ggcacactgt cgagaacaaa 360  
 tcctcctact cagaaaccgc caagtcctcc catgtcaggc cggggaacac tgggacggaa 420  
 tactccttat aaaaccctgg aacctgttaa accccaaca gtccctaata actatatgac 480  
 cagtcctgct aggcttggaa gtcagcatag tccaggcagg acagcatctt taaatcagag 540  
 accaaggaca cacagtggaa gtagtggagg aagtgggaag ttcgaggaaa acagtggtag 600  
 cagtagtwtt ggctwtcccw ttgctgtgcc tacaccttcg gcaccayta ttttgaaacc 660  
 atttgttgat ngttccaatt tccaccgna ccactttnc ccaaa 705

<210> 106  
 <211> 920  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (920)  
 <223> n equals a,t,g, or c

<400> 106  
 gctagaagtg gattggagcc tctttgatgg atttgcagat gggtaggag tggctgaagc 60  
 catttcctat gtggaccctc agttcctcac ctacatggca cttgaagaac gcctggccca 120  
 ggcaatggaa actgcccttg cgcacttgga gtctctcgca gtggatgtag aggtggccaa 180  
 tccaccagca agcaaggaga gcattgacgc tcttcccag atcctgggtca ctgaagatca 240  
 tggcgagtt ggtcaggaga tgtgtgccc catctgctgt agcgaatatg tgaaggggga 300  
 ggtggcaact gagctgccgt gccaccacta tttccacaag ccgtgtgtgt ccatctgggt 360  
 tcagaagtca ggcacctgcc ccgtgtgcc ctgcatgttc cctccccac tctaaagacc 420  
 aaggccgttt actcctggtc tgattatatt ccccatctga aatccacaat actgcaggag 480  
 ccctcttgaa attaacaatg gaaataaaac caatcagtca gttagcctaa acctattgat 540  
 tcctcgtgat tatttccaat gtgaaaacag ttgtgtatga ttgcattaaa aatcatatca 600  
 tcttttagag gttagaaaag ggaaaactaa actttctaaa tgctacttga gattgcagta 660  
 agaagatacg ttttctaacc tgaaagttaa atcgcatctt ttttcttcag tagaatggga 720  
 atgtgttgct gttacttgta atgtcaagtt tatctgttaa atatgtccaa aaggcaaaat 780  
 catttttggt gcatgttatg ggtcgatgtt cctgtaattg cagtgccgta aaagcttatt 840  
 aaagttgttc ttttggtttt aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 900  
 accccggggg ggggccgggn 920

<210> 107  
 <211> 466  
 <212> DNA  
 <213> Homo sapiens

59

<220>  
 <221> misc feature  
 <222> (1)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (7)  
 <223> n equals a,t,g, or c

<400> 107  
 nggccentac tcgggcgctc ccagarggag ccacctctca gtgcctcamc tccccctgcc 60  
 tcccagcctc cgcagatgag gttcctgccc cttcctcctc gtaacccaaa ccctcactgc 120  
 tcccaggacg gtcttattta taaaccagat acatgttctt agtctgggtcc cagaccaagg 180  
 agctgggtcag acggcccttt ctaatcctac atgttgagct tatgtaaaaa atgttggttc 240  
 ctctgttttt tgggttccttt cttaccaca aaccattact acttgaaact taaaaaactc 300  
 gccaaagtgt aaggctaaag agaagcagtt tgacggacct tgtgatttgt actgtttgct 360  
 gcggagctat ttaaagattt tggaataaat atacaaaact acggttggtga aataaaaact 420  
 taaattgtat attttgaaaa ataaaacact gaaaagaaac aaaaaa 466

<210> 108  
 <211> 323  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (111)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (113)  
 <223> n equals a,t,g, or c

<400> 108  
 actatTTTTTT tATTTTTATAA atCTTTTGTAG aaATAAGCAA tgAAATACTA cTTTcATcTT 60  
 ttGAAATGGG aTTTTTCAAG gcAGTGTcCT tTTGGCATTa agGTAGGGGG ncnGTtaATA 120  
 ttCTcTcTgc cTTgtttCCA cGTgGAATCA atATTAAAGT catGGACATT tTAAATcTc 180  
 aATTtaATTT cTTcTTATTT actATgcAGT atAGccGTgG aACAAGTAAT gTAGATTTAG 240  
 tTTTcTcATc tTCAaATGCC cTgATcACCC tAcCTcACAG gGTTgTTGTg gGgRTwaATA 300  
 aaACTTTATg grAGCAAAAA aaa 323

<210> 109  
 <211> 448  
 <212> DNA  
 <213> Homo sapiens

<400> 109  
 ttttttcaca gcatattaga aatgtttatt aagaataatg gcatgaactg cttttaacaa 60

60

```

tttagaaaag acccattccc cccgcccsc cccgccccca gatccagggc acttcctcta 120
agtaaayaca aatatttctg tagtgaactg tatgcatatt cccactgagt aaagggtata 180
agaagcctca ggtcaggtct taccaccaa cttgaaaaca cttggaatgc agctgggcag 240
ggacttgagc aggttttctg ttgataagca ggtaagaatg gcagaacact ggcttattgt 300
caaccaatgt ttttttatat acctgaagta ttcacagcaa cttattttta gaagcttttt 360
aaaagttcta cacctccacc cccacaactc cccaatccag aacatggaac aagggtgtgg 420
agccgtttga tggacttggg tctgttcg 448

```

&lt;210&gt; 110

&lt;211&gt; 849

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (32)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (33)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (39)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (841)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 110

```

gggtgactccg tctcaaaaaa aaaaaagaag gnngtaccna cagtatacgt gtggggcactt 60
gtgcttgagc ctgtattaaa ggaatcaggc caggcacagt ggctcacgcc tgtaatctca 120
gcacattggg aggctgaggt gggcggatca cctgaggtca ggagttcaag accagcctgg 180
ccaacatggt gaaaccccat ctctactaaa aatacaaaaa ttagctaggc ggggtagtgc 240
atgcctgtaa tcccagctac tcaggaggct gaggccggag aatcgcttga gcccagagag 300
tggagactgc agtaagccaa gatcatgcca ctgcactcca gcctgggcaa cacagggaga 360
ctccatctca aaaaaaaaaa aaaaaaaaaa aagacattca acttgaggct cctgttagtt 420
aagctatctt ctttcacttg aagcaggttt gagaggccta ggccagaatt taaattcctt 480
ttatgaatag atttcccttt cttctgacc ccaaggtcag aggagactat atattccatg 540
gctgcctcta agactaggaa taggaatatc tgaaaacagc atttctaagg gtggtaacca 600
caggctgatt ttaatacgag tcctttttct tgtagaggta agtaaaatct tcctgacaag 660
gtagtctctt tttcacggca cagacaatgg gctttctgtt tatgaggggt gagaagtgat 720
gtttgttact atgttctcca gcaagtaaac attcctctgc tcacctcca acaagactaa 780
cagtcttttt agaagtaa atattcaaga caaacgagaa aatcctggct acccaagtcg 840
ngtatatac 849

```

&lt;210&gt; 111

## 61

<211> 876  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (871)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (876)  
<223> n equals a,t,g, or c

<400> 111  
aaaaaaaaatt tacaaaaaaaa caamcacama aaaawtatct ttttttaggcc agagttttct 60  
acaggtatta atgaatatatt ttcttaatcc ttataagttt tatgtgttta atattttctta 120  
ataccggttag cattaattta tacttttgta gcaacacaat atttttataa acagccggtg 180  
cttggtcaa gtcttcacga ggggtttagg cagggccatc ttggggaccc tgtgtaccat 240  
gtactgtatt taaaaaaaaa aaaagttacc tattgtcaca cttgctgtgt taattaacaa 300  
aagatgttgt gtgcggtctc ctgtatcggg gtggatccaa cagctctcca gggagtcaca 360  
ttgcatgggg gttgagttga cggttcttgt gatatgtaaa ccccgagac caaacttgag 420  
ggtttattta gggttttctg tttgtccttt gggtttttgt ttcactttgt tttggtgccg 480  
tttctccatt tacagccaaa tcagtttcat gatgttcaaa acatttactg atgtcaaattg 540  
gaggaaagga acagaaaaaa agattttttac aaagtaataa aattttaaac tgagctgttt 600  
aatgttgctg tttttacctg tctgttcttg tccaaaagtg gaacattccc agggagaaga 660  
ggaaggttcc actcgggttct ttaagtcgcc aaaagcccca gcccgggatt cagtacctcc 720  
cctgcccccc gaattcttgc agcactatct cccagttggt tgatgccaaag gcaaaaagat 780  
aacttttaac agttagagag gatcagttgc ttaaattgatt tcatgtcagt gttgtattta 840  
tggttttaca ataaaacaac ctttaggaaa naaaan 876

<210> 112  
<211> 382  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (100)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (105)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (341)  
<223> n equals a,t,g, or c

&lt;400&gt; 112

```

gcctcccagg ttcattgcat tctcctgcct cagcctcccg agtagctggg actacaggca 60
cctgccacca caccgggcta cttttttata ttttttagtan agacnggttt catcatgtta 120
gccaggatgg tcttgatctc ctgacctcat gatccgcca ccttggcctc ccaaagtgt 180
gggattatag gcatgagcca ccgtgcccg ctattttcag ttcttatgt gtgaaccact 240
ttgccttgta gctttttcta tctttccaaa atcctcactc tggtcattgt ttgtctcagg 300
ggaaaatctt cccccaccga gcttgtaaaa aaactttaat nattgggtgg aggataattt 360
aggatgggta tttattggag gt 382

```

&lt;210&gt; 113

&lt;211&gt; 1070

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (334)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (882)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (961)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1018)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1070)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 113

```

ggcacgaggg ccgactggac tttgtgagct ccagctgcta cagttgactg agttcaggct 60
ccatgtagct gggatatact acatggttac ccctcaccct tatggagctt ccaaaagaga 120
ccctccctca aagcacagcc ctttctctga gtgcaaataa tggccatcag aggtcagtca 180
cagggtgtag gcaggcatct atgaagctgg ggatgatagc actgacttca gtgcttggac 240
gagaaccagg agagagtgtg tagaaaaagc acagccagcc tcccataaaa ggacagaytc 300
ctgtgacaac cttgtcactc tgttctctcc tgantactct ggggaggtgg aggccagtgg 360
gcagttctaa agctcagcag gtttggagcc attgggtgtg gactcctctc ccagtgttcc 420
tcctgggtgt tcacagatgt tattgaaatg cacactggga accctgcaca ggtaaaacta 480
aggytttatt ggcgtgattg ccaaaggtea cacagggtgg tttggyagag ctgggattag 540
aagcccagcc tgytctytc cagtagtaat ggagtcctgg gaggtttact aggccttagc 600
ctcaatctgt ggcggcaggg tccacagccc tggggagtgga cacagtcatg gtcccatga 660

```

## 63

```

ttggccagga cctgtktgga gagacacagg agacaagacc ctgctcttcc aggccagaag 720
ggaggggagc cccagagctg ggcagtggca tgccccacag cctggccacc tgcttcggct 780
acgcaccatg cagcagctgc acctggctgc ctcgggaaaa ctctgacctc tctgggaagt 840
ggagccagtg gctctgtggg cgtcctttcc tgcagcctgg anagcaaagc ggctttccct 900
gggactgtgt ggctcctgtc ccaactggcc tccccattcc acattcccat tgctggacca 960
ncaccaggac tgggcacagg gcttcctttt gctgattcat tcccccccta actcatcnaa 1020
attgaacccc atctgattcc cacatgctgg ccctgaaacg gtacaaagg 1070

```

&lt;210&gt; 114

&lt;211&gt; 371

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (360)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 114

```

gtctattaga aaacggtcct aagagattct ttggtgtttg gcactttaag gtcacgtttg 60
ggcagaagtt tagcattaat agttgttctg aaacgtgttt tatcagggtt agagcccatg 120
ttgagtcctt ttttcattgg ttttcataat attttaaaac tatttggtta gcgatgggtt 180
tggtcgttta agtaaagggt aatcttgatg atatacataa taatctttct aaaattgtat 240
gctgaccata cttgctgtca gaataatgct aggcataatgc tttttgctaa atatgtatgt 300
acagartatt tggaaagtta gaattgatta gactagttaa ttttaaggagt atttgaagtn 360
gggtgggggg g 371

```

&lt;210&gt; 115

&lt;211&gt; 581

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 115

```

tttttttttt tttttttttt ttttyttgagt attccagcat tatttatttg atcagagtaa 60
aatacacttc ccatcactac aaactgagca caactacagt tgtctacaca ttcataatttt 120
tgacgtgcc aacattttgca ttctacatga aacattttgg ttaaacaata tcttaagaat 180
tctctatttt gtttcccatc ttccctcctg ttctctccca tctcccaaag atgttttata 240
ttaactgcta tgagatttat ttgccgggtc cgtaatacgg aggacagcag ggaacaacac 300
aagattttacc atgcctaggg gatgaatggc aaacccaact ttggctaatt tcattgagaa 360
caacttgga agcgtgasag gaggatatct catggaagtg ggcagtgaac ctacatttcc 420
atttatcaga agcaaactg ggaagggttac atacatgatg aagtattgga agttaagac 480
ttaagacaca aaatcactaa tttaaaagra cmtgcmacmt grgtatcaac ttgctatgta 540
gkgtagatgt aaatgaccca aatattcacc tctagcatcc g 581

```

&lt;210&gt; 116

&lt;211&gt; 705

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

64

&lt;222&gt; (681)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 116

```

atcggacggg cttaacatga aagcctatag gtcattcttg ctctgggatc tacaggcagg 60
gtaggcacag gtgcagccta agaagggaac ctgcttcctc tcccttccaa agacagtga 120
agctgactga gggcaaagag caggcaccac tcagaacgtg gtgagtacag ctcagctcag 180
cactcagtca gtggtaactt gtgcccagcc ctgtgctagg cgctgacatt aacaggagca 240
accaggggccc aattcctggc cttggagctc aaatctttcc tttgattttt gtccttgatc 300
atcaaggccc cagtggcaac catgtggtaa gtggccaacc aagccctacc cagggtcacc 360
caacacactc tgccttgagc ctctcctcag ggtctattcc ttgctggtat tatgtggccg 420
tagcatgtta cagttcaaac atgtctccac taccctgtta agagcagcct gggaaacgtac 480
aggccatcaa gactatttat tttaaatacaa aaaaaggggg aaacacacac acggaaaaaa 540
aattgtaaagc actttttttg taaaaccaat gtctgttttg ttacatacct ttcattgtcgt 600
gctttgtaaa tgtcttattt gtgtaataaa gttaatgcaa gtaaaaaaaa aaaaaaagat 660
gggcgaagtt atcccttgtg nggtaattag tttgctgcgc gttta 705

```

&lt;210&gt; 117

&lt;211&gt; 1196

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 117

```

gcgaccgcct cgcgtaccgg gcttgccggc cagcagcgag cagccccggg gtggcgatgg 60
ggtcgcgcgg aggcagcggg ggttctgcgg gcgactggag gttggcagtg ggcgggagaa 120
agaggaaggc aggcgcgggt gggcctcggc ctctggcgcc gcggtaccct ttgtctcggc 180
agcctgacgg cccgcgcggg ctctccggag aggggaacgg gcggcgaggg tggcgggtcc 240
tgggcgcctt gtgctgcggg gccgagaggc gctcgggtcg cggcgggatc ggccggacca 300
gacagggtta atggaagagc ctggccagtc ccgcgcgggg ccccgccagc gacagccttg 360
gccgcgggga ctggagtcct gagggggaga agcctgccgt tctgaaggct cgggacttct 420
gccccaaaga cttgcgcgcc gagaactgcg ggtgcactgc ctcagggaag aagttgagaa 480
ttttgccagg tcatctctgc cagggcacag ttcactactg tgtgtttagt gtgtttcggg 540
gaagctctcc aagtgtgttg aatcagcgtg cctagcctca aggggtgcac gtgaaaactg 600
aaaccaaagg aatgatacag gcctgctttg tgtgtgtctt cccactttaa gcttggtttc 660
agtacaaata ctcttgcttt aaacctgatt ggactgtggc gagcggacat ctgttcaaag 720
gagggggcga gaccacagta cttctgaagg gggcttgata atgtggaaac attttaagtt 780
ttctctcggg actgttttgc tctctcaatt caggcaagtt actgaagtac gttttttatc 840
tagaaaaagg tttgatgtag tctgtaaatg gtccttgtaa agtacattgc catctcagaa 900
ttaaaagatc cactctcatt tattatgcag aagttagtgg tcattctttc ctgtagatag 960
tttatctcat gtaaagaccc acccagcttg gtttaaattt tttctcact gacgtataac 1020
catcagcttt gatacttcca ttttcaggct cagactttga atttaaggaa actaaagatg 1080
actttatttt cttttctctt gggttttttt ttccaaaaac aaaaaataaa tccattacat 1140
gttaacataa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaacggacgc gtgggc 1196

```

&lt;210&gt; 118

&lt;211&gt; 975

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature



65

&lt;222&gt; (794)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (845)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 118

```
tgtccctttt tattctagag gcttttcctt taattcagag attagtggag ataataacgt 60
cagtcaaggc taatgtggta catggaactt gctaattggag gttggacatt ctgttttcagt 120
cttacatgga tattgttttca ttggtgttga ggaagaaaaa aattagatac taccatgcat 180
tgggacagca taattctaatt attacattga atatggcttt ttaaaaataa gtattaaaaa 240
gccaatcggt ttctccattt atctatcttt tttgtttgtt ttttaatttg ttgattgata 300
tgcaccagg ccgtcttatt ttacttggt aaatgtctgt ctaggaagaa ctgtgattgg 360
aaaggaatta attattatac aaataaatct ggtaggatat gagtggagta agtttgcttg 420
aaacagaagt atattttcta ctttgaatca cctcaccaga gtcattctgtc aagaattatg 480
tataacaatt tatctttatt gcctacatac aacatacttt ttctgaatta agataacttc 540
tatttgtagg ttgaacttca ttatctgcca ttttgtggaa tcaaccttac attytttggt 600
ggractagag ctgattgtca ccacaagggt atatgacaac tctgttctar grcttatacc 660
yattatatag ggktatacct tttttcttat gcctcagctc tgtacctgac aatttatgat 720
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gtctgcttat gcttt 975
```

&lt;210&gt; 119

&lt;211&gt; 331

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (331)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 119

```
catatattag tgtgctttga agttgactga aagatatact ggatatcata attatataat 60
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tgactattgc acttggtcta ttgttttaat agtaaatttt gttattaatc tcctatgtgt 180
taaacgtggg taattgtatt atgttaatac atacttaggg aggaaaagca ggtggatgta 240
aatcagtgat tcccaacttc agcagatggw tagcmgtggg aggggtatcct tggagctttt 300
tgtaaatatt tccaaaaaag gggggggggg n 331
```

&lt;210&gt; 120

&lt;211&gt; 233

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 120

## 66

```

tcgaccacag cgtccgcccc cgcgtccgca aaactgagag ggataggaaa gaaaaactta 60
tccaggaagg aaaattggat cgaacatttc acctctcata ttaagtctgg caatgatgac 120
tatatgtatt cctgcctaaa taaatcatct attaatacatt aaaaaaaaaa aaaaaaaaaa 180
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aagggggggg ggg 233

```

&lt;210&gt; 121

&lt;211&gt; 2043

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 121

```

ggcacgagca gccctcggcc ccaccctac gaccagccct tccgtcctgc ccaccccggc 60
agcgactggg gttcctgaag acacataaat ccgggagcag ctctgtgctg agcctgcttc 120
accgctatgg ggaccagcac gggctgcgct tcgccctccc tgcccgtac cagtttggct 180
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aaa 2043

```

&lt;210&gt; 122

&lt;211&gt; 2877

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 122

```

tcgacccacg cgtccgggat gagggccggc ctctcatttc tcctagccct tctgtttcttc 60
cttggccaaag ctgcagggga tttgggggat gtgggacctc caattcccag ccccggtctc 120
agctctttcc caggtgttga ctccagctcc agcttcagct ccagctccag gtcgggctcc 180
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cccgtggaca gagtggaacg cttggaattc acagctcatg ttctttctca gaagtttgag 360
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ttaaacctaa ctgtccgaat tgacatcatg gagaaggata ccatttctta cactgaactg 480
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68

<210> 123  
 <211> 681  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (101)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (223)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (224)  
 <223> n equals a,t,g, or c

<400> 123  
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 ggcagcttct tcgatcaagc tgacattatg ggattttgtg nccttggatt cacgacacac 120  
 aaaacagagg aacttcccat catcctcgca gaaatagtgg aacatctcct ggtgcctcgg 180  
 gcaatgtagc ctcttttctt tttggactgc acctcagagg ctnnngtagag ctttggattt 240  
 tctccaccag attccgcaac agcgagtgtg acctgattgc gttcttcctt acggaagttt 300  
 tgcagagggg acatttgaaa aatccacatg atgtttcccc aatctgagtg atgcatttga 360  
 ggcagaaatt gtgcccacag tcgatggtga cagggtttctg cagaatgtcc aggcagatgg 420  
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 ccaattagtt agaagagcag agagagagga aaagaagagg gagaaaaaaa taaagaaatg 660  
 atagaaaagc gtaaaattta g 681

<210> 124  
 <211> 606  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (34)  
 <223> n equals a,t,g, or c

<400> 124  
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 tgcttaatga aaatgtcagt tctaatagta actgattcac ttctgaacag aagtgatttt 120  
 aggcataattt cttaacatat atcaagcaaa gtcctgttaa aagatctaaa tgaagaatgg 180  
 agacctcagt gattaaagat attttgtttc tgaccttgag cagattgctt acctgttctc 240  
 tagactataa cccaacatgt aaaaaaatt tgaagatggg gatgaggaaa gtgagatata 300  
 tatatatata tgtattaygt ttctagcact tttccctttt aaaaagtga aatataccttg 360

69

```

tacattttttg aaaaatatat ttycagtyct gaaaaatgta gcagaagtag tgaaaaatgyc 420
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ctttcagacg tgtgttttygg agtagtggaa ttgccagcca ggccctgtgg cttggaaagg 540
catcccagaa atcctcggcc agaaggtgtg gcttgttaaa gcattgagat tcmgagtatt 600
ttggtt 606

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&lt;210&gt; 125

&lt;211&gt; 1211

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 125

```

aattcggcac gagagcggcc ttcctcggtc aagtcgctgc gctccgagcg tctgatccgt 60
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caggagatct cggtgctgaa ggagctcaag gagcagctgg aacaagccaa gagccacggg 180
gagaaggagc tgccacagtg gttgcgtgag gacgagcgtt tccgcctgct gctgaggatg 240
ctggagaagc ggatggaccg agcggacaca aggggtgagct tcagacagac aagatgatga 300
gggcagctgc caaggatgtg cacaggctcc gagggccagag ctgtaaggaa cccccagaag 360
ttcagtcctt cagggagaag atggcatttt tccccggcc tcggatgaat atcccagctc 420
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tgaacattga ctgtggctaa agttatttat gtggtgttat atgaaggtag tgagtcacaa 540
gtcctctagt gctcttggtg gtttgaagat gaaccgactt tttagtttgg gtcctactgt 600
tgttattaaa aacagaacaa aaacaaaaca cacacacaca caaaaacaga aacaaaaaaa 660
accagcatta aaataataag attgtatagt ttgtatatatt aggagtgtat ttttgggaaa 720
gaaaatttaa atgaactaaa gcagtattga gttgctgctc ttcttaaaat cgtttagatt 780
ttttttgggt tgtacagctc caccttttag aggtcttact gcaataagaa gtaatgcctg 840
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aaaaaaaaaa a 1211

```

&lt;210&gt; 126

&lt;211&gt; 881

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (7)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (16)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

70

&lt;222&gt; (34)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (37)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (41)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 126

```

tatgatncct cgctcngttt ctgaaatttt cacnttnac naggtttcaa catataaact 60
ttcaggggac acagacattc agactatagc accaagctgt agaagctaca tagttgtaga 120
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gggmctaaac maaattctka ggccccctca accatctaaa tggacttcct tctgggccag 360
gacactcgaa aattaaacct gaaagactgg ttcaggccat gatgggaagt gggagtcgaa 420
catgcctcat cataccctcc agcattaaca tcaacacaga ccttaaggct gataagaagc 480
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ttcaaatatt ttaaaaaaaaa aaaaaaaaaa aaaaaactcg a 881

```

&lt;210&gt; 127

&lt;211&gt; 917

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 127

```

ccatcttcac attttgcttc catatttgaa gagtctcag tgccagtaat tgaagaatct 60
ttgagagttc agatatgtga aaaggcagaa gaattaaagg acattgtgcc tgaaaagaaa 120
agcactttta atgaaaatca gcctgagata aagcatcagt ctcttctcca gaaaaatgtg 180
agtaagaggg atccaccag cagtcatggg cacagtaaca agaaaaatct attaaaagta 240
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aagactacaa gtaagaagt atctgaaaat gaaaaaggaa agaaagtaac cacaggagaa 780
acaagtctta gtaacgataa aataggagaa aatgtccagc tatcagaaaa gagggctgaag 840
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gaggcagctg tacaaaa

917

&lt;210&gt; 128

&lt;211&gt; 1287

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1142)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1233)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1265)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1271)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 128

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tttaaaaacc cctggagggt ttaaccttgt gatgccttta tgaatatect gttgaaatat 60
ccttccccct atgccttata aaccagagaa agccctttga agccttataa tgccaatgga 120
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ttaatttggg atttttgaaga ttctacagta ggaaacgtcc ccaataaggk aactttttca 1140
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ttttnaaaat nacaattgtg atgaggt 1287

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<210> 129  
 <211> 603  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (391)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (517)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (580)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (602)  
 <223> n equals a,t,g, or c

<400> 129  
 cgcttgggct tggcgggtat aggttgcagt gagccaagat ggtgccactg cactgcagcc 60  
 tgggtggctg aacgagactc cgtctcaaaa aaaaaatcta aatctgacat ttgatgctat 120  
 ttttattaat attggaatgt tctgtcttga actttattca atataatcaa gaataaagat 180  
 agagtaaacg tcaactgattt gtactattaa gagagaaaaa atatgccaca caactaaaca 240  
 taggtttaaa ttatgaagaa atttagaata gaggtttatt agatttaggg aacactaaga 300  
 acaaaaaagg aaggagtgat acctgcctga gtggacagct gtaaatacagc tgtaattact 360  
 gcagttgtwc caatagttgt gartggctcc nagtcmcttt argagtcctt ggaartwctt 420  
 ggtacacatt tgttggctgt wccttaaagg aartggcaar tccagtttgt tcycctctacc 480  
 aactaract gccactgaca agtttgggtc tgttggnttc aaaattttgt aagccatttt 540  
 cacaagtaca aagatacatt ttaaccttgt cttctccaan attactgagt aggaatttta 600  
 tnt 603

<210> 130  
 <211> 532  
 <212> DNA  
 <213> Homo sapiens

<400> 130  
 ccacgcggtc cgaagagagg ttggtagaaa aactaaaact ctacaatcta tttcttaaaa 60  
 ataatgtttt tcttttcttt ctttcttttc ttttctttct tttctttact ttttttttc 120  
 ttttcttttc tttttttttt tttgacaggg tctggctcta tagtcaggt tgagtacagt 180  
 ggtgtgatca cggctcactg caaccttaac ctctaggctc aagtgaccca cctcagcctc 240  
 ttgagtagct gggaccacag acacaccacc atggccagat agttttctgt attttttctt 300  
 tgtagagaca gggtttcacc atgttgccca ggctggtctc aaactcctga gctcatgtga 360  
 tctgcctgcc tcggcctccc aaagtgtctg gattacaggc atgagccacc acatgtggcc 420



## 73

catttttttct tcataagtga gttttagatt tttactttgt tctaattttt tgaggctatg 480  
 ttcaggaagc catcacagctt gaataagtaa ccatctcagg agaaaaaaaa aa 532

<210> 131  
 <211> 776  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (630)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (669)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (769)  
 <223> n equals a,t,g, or c

<400> 131  
 aatcctcagc cattttgtga aaatagccaa gaaacttcta gaactcaaca accttcattc 60  
 tctcatgtct gtggtatcag cattacaaag tgctcccatc ttcaggctga caaaaacctg 120  
 ggctctttta aatcgaaaag aagactacct ttgagaaatt ggatacctga tgtcgaaaga 180  
 agrtaattac aagcggacac gggaatatat ccgargcctg aagrtgggtc caagtattcc 240  
 ctatctagga atctatcttc tggrrtttaat ctacattgrt tctgcatatc ctgcctcagg 300  
 agtaatcatg gaaaatgaac aaagatccaa tcagatgaac aatattcttc gaataattgc 360  
 tgatttacaa gtttcctgca gctatgatca cctcaccacc ctgccccatg tgcagaagta 420  
 cctgaagtcc gtacgctaca ttgaagagct ccagaagttt gtggaagacg acaactacaa 480  
 actgtcgtc agaatcgaac caggaagcag ctctccaaga ctagtctctt ccaaggaaga 540  
 tcttgacagg ccctctgctg gctccgggtc tgcgagggtc agccggaggc acctgtcctg 600  
 acacatctgt tgctggcagc ctccccacan ctccagtgcc cagacacagg gaagagccac 660  
 agcctaggna acaatatgga tgtgttcagt tgagtgttag ttgaggagta aaagtgcgac 720  
 atttcccttc ggagaaaggc aagggcacct acttggacga cagtgttcnt agagtt 776

<210> 132  
 <211> 689  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (348)  
 <223> n equals a,t,g, or c

<400> 132  
 atcagggacc cttttgatcc aattatagtt attgggcaga tacagtagta ccctattatc 60  
 agaagaccta gtttcaaadc ctgagtcaat ttctaattca ctgtgtgacc ttgtacaagt 120

```

cacttaagct ctctgatcat tggttcaaca tctttaatat gaggagagta atgcctatct 180
caattacctc ataaaattat tgcaaagatc aagtgagttg atatgttaca aattatttct 240
aaattataag attctgtata agtgaagggg ttaagtatac tcccatatta ttaaaccacc 300
tacgtatcac tcaggattct atatgactct gagttctcaa tttctagnaa atggtcccat 360
ttttgctttg ttccctacaa ttctacggag tctttttttt ttwaaaggaa ggggtgtaggc 420
aaaggtaaat gggagaaaac atggaatcac ataccactct ttggtgctgc taggcaagaa 480
ttttaaaactg agtttaggtc accatcgtgg acttaagggtc catatcacct caggagagaca 540
agtagagtgg gaggcacca aaaggtaggt gattcttctc ccctctagtg aagaatacaa 600
ggtcaattta caaaaaagca ccagcagcaa ataattggaa aattaaattc ataaamcatt 660
tataatagcg tcaaaaaaaaa aaaaaaaaaa 689

```

```

<210> 133
<211> 555
<212> DNA
<213> Homo sapiens.

```

```

<220>
<221> misc feature
<222> (4)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (36)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (308)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (471)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (484)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (489)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (510)
<223> n equals a,t,g, or c

```

75

&lt;400&gt; 133

```

ttcntgccccg ccccatcctg tgctttggcg taggcnatca ctgaagactt tctattttctc 60
cattagttca ttcattcttg tagctagact catgacggag ctgctgccac cccagcagat 120
ctgctcgcct tgctgcttct tcacggtctc cacggccttc gcagaggtgt cagcaactgc 180
catgaccact tgcagcagtt ggctgtagga agtcagattc tgggtgcgtgg cctggatgat 240
ggggccgcac ggggtggaggt cagggccttg gcgctggcag cactcgccca gctcgtcgtc 300
gtagattngg agaaaagcca agattagctg gtggaagtcg gaagtgacca gacgcagctt 360
ctggtctagg gtgctgatgt cggctgcgcc cgcaaarccc cttgcttcat gctgtgcaaa 420
ktactccgtt tctaaagcgc gtgcaattgg gcagcattct cctggcagtg nctgggcaac 480
ttcngccanc tttttcttct tcttcggaan ttggcaaagg catgggcca atggccatca 540
tcaatctggc ttgtt                                     555

```

&lt;210&gt; 134

&lt;211&gt; 790

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (776)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (780)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 134

```

gcaagaatat aaaattctga ggcctatttt agctctaagc cagaccatgt tataactttct 60
taactgaata cttcttatct atactttttt tctatatctt tccatctatc tgtaagtagc 120
ttttcccatg atctgacttg tttatatttc ctattaactg acaaagcatt taaaaacagt 180
taaaaattgt ctgcagaggc attttaaatg tcaagacatt ataaaatact ttagatttat 240
acagcaattg tgaacacctt tgacaaatga acatgtctgt tcagcctttt tgggtaccct 300
ttttattttg cttaggtaga tcaaattcta agttgatctt ttctagcagc agggtcagag 360
tctagtgatc gtttttaaaa tggcttagat gctaccttc ttttctgaga actcagtgtg 420
atataatcct tataagatat tgacagctaa ttttatggat tatectaccg ggacagtgga 480
acctaagtag tttgaagacg araaattgtt ttgattcaka agcaatgggt tcaactagtga 540
aaggaaagat cccacgatcg taagtggtaa atgtttatat ttgttgaata actctctgaa 600
aaaaggaaat aaagtagatt agccttggtg agaggtggct taagagtggg tttatgaatc 660
taagttttat ttgaaaaatg tgtgaacttg ttttaaggtaa atgtgagaat taataaagga 720
attgagaaga aagatatattg atcgtttttt ggaataacat ttaccaat taangangtn 780
aactactttt                                     790

```

&lt;210&gt; 135

&lt;211&gt; 1408

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (116)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1364)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1381)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1393)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1399)

<223> n equals a,t,g, or c

<400> 135

```

tttgccagct ctgaatcttt attttaattg atctttttat tgatgtgtta tataaatgag 60
gaagaaaaat ttgtgtctgat tatgtgaagg atctttctgt acatgaaaag aagggnaaat 120
aaacttgcaa ttgaatagac tgattatagt agcactgaga cacaaaaaga ttgaccatgt 180
tgccctccag acactcatatc aaggtcgtgg acaccagggt gaaggcggac tatttaggggt 240
ggtaaaggaa ttatgattgt tcttgagcca aagtaattta gtttgaatat aatgaaacat 300
accctgtaaa gactcttaga aagtaaaaagg attcgtcttc agagggttga gaagggtgcc 360
ttcttagtta aaaccaaact gggaaaagta atactggata aaatattcag gataaatttt 420
gcctcagcag aatttcaaag ggcagttgtt cctctgtttc attattgaat sttcagaata 480
tagttaaagc caaargctta aaatatgtta aatgtttcac ttataaccat aatcttttta 540
catagagcat actctgcctt cataataact aaatcctctg catgtggtag atgagtacgt 600
ttaggaaata ttgtcagtcg aattaaatgg cctacacttt aaacagtatc ataaaaacaa 660
atccttaa atattctact tgagtcacaa aagctgaaca acagaaagggt gttttgtttt 720
tgccctttctc acagtgttgt ggtgagaatc agatgagata gtatttkgac taaacacttc 780
tgaaattgta aatatatggg ggcattattg ttcttatgtc ggcttaggag gataccaaag 840
gggaagttaa tggtcacagt gcacttatgt agctttctaa gctactcaat gtgattcttg 900
ttctctttgc tgttcttttt ctctccccc atggtgtcct tcagagagaa aaggaatgta 960
gataaatgaa tccctgcaga tgtgtcctga catttcaggg agggacaggg tataatgatg 1020
ccatcctgca aaggcagcct gtgtgagaaa aagaaatcaa ataattgtga ttttaaaatt 1080
acaaaagaca ttcatttgca gtttatgaaa ggaaaatgta gtttggatac aaagctgatt 1140
aaattggatc aagaaatatt agaattaaat gcaaaaaata atccatgcat ttatggtttt 1200
gatttttata tattccagc tagttgaaaa tggatgattc ccacaagaag cataactcag 1260
cttggttctt gcttaccgga gtatttccac tatggtatat attgatacat tccttccatt 1320
atggttaggt gtataaccaga ggtaccagtt accggtgggg atcntaattg gaattttggc 1380
nccccggggt ccngggganc ctttacia 1408

```

<210> 136

<211> 902

<212> DNA

77

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (814)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (902)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 136

```

aattcggcctt tcgagcggcc gcccgggcag gtacttataa ttttggcctt ctgcactact 60
cttttgctct tacgaacata atggactctt aagaatggaa agggatgaca ttacctatg 120
tgtgctgcct cattcctggt gaagcaactg ctacttgctt tctatgcctc taaaatgatg 180
ctgttttctc tgctaaagggt aaaagaaaag aaaaaatagt tggaaaataa gacatgcaac 240
ttgatgtgct tttgagtaaa tttatgcagc agaaactata caatgaagga agaattctat 300
ggaaattaca aatccaaaac tctatgatga tgtcttccta gggagtagag aaaggcagtg 360
aaatggcagt tagaccaaca gaggcttgaa ggattcaagt acaagtaata ttttgtataa 420
aacatagcag ttttaggtccc cataatcctc aaaaaatagtc acaaataata caaagttcat 480
tgttttaggg tttttaaaaa acgtgttgta cctaaggcca tacttactct tctatgctat 540
cactgcaaag gggtgatatg tatgtattat ataaaaaaaa aaacccttaa tgcactgtta 600
tctcctaaat atttagtaaa ttaatactat ttaatttttt taaagatttg tctgtgtaga 660
cactaaaagt attacacaaa atctggactg aagggtgtcct ttttaacaac aatttaaagt 720
actttttata tatgttatgt agtatatcct ttctaaactg cctagtttgt atattcctat 780
aattcctatt tgtgaagtgt acctgttctt gtcncttttt tcagtcattt tctgcacgca 840
tcccccttta tatggttata gagatgactg tagctttcgt gctccactgc gaggtttgtg 900
cn 902

```

&lt;210&gt; 137

&lt;211&gt; 730

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (606)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (647)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (671)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (685)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 137

```
tacttcagat acactagtaa agcctgctgt attccaacta atgaggacag atatgtaata 60
tatatacatg tatatacgta tgtatgtata tatactatat atataattat actttaagtt 120
cctaaggtag atgtgcagaa tgtgcagggt tgttaaatag gtatacatgt gccatgggtgg 180
tatgctgcac ccatcaaccc atcatctaca ttaggtattt ctccctaatgc tatccctccc 240
ctagccaccc acccccagac agggcccgct gtgtgatgtt cccctccctg tgtccatgtg 300
ttctcattgt tcaactccca cttatgagtg acaacatgcr gtgtttggtt ttctgttcct 360
gtgttagytt gcwgagaatg atggtttcca kcttcatcca tgwccctgca aaggrcatga 420
actmattctt ttttatggct gcatagtatt ccatgggtgk tatgtgccac gttttcttta 480
tccagtctat cattgatggg catttgggtt ggttccaagt ctttgctatt gtaaatagtg 540
ctgcaataaaa catacacatg tctttatagt agaatgcaca tgtctttata gtagaatgat 600
ttatantcct ttgggtatat aaccagtaat gggattgctg ggtcaanggg cattctggtt 660
caagatcctc naggattcac cacantgtgt tccacataat ttaagctatt ttacactccc 720
accagcagtg                                     730
```

&lt;210&gt; 138

&lt;211&gt; 524

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 138

```
ggcagaggag gccactgtgc ctgggtcaaga aatggaactc ttacacactg ctgggtgggaa 60
tgtgaaatgg taagccactt cggaacacag tttgacaatt tcttatgcta aaaatacacc 120
tatcagatra tttagccact tctaggtatt tacttaagaa aaaataaggc atacatccat 180
atgaaractt gtaaataaat gttctcatta tttttatttg aaatagctma aactggaaac 240
aaccacaaata tccatcagca agtgaatggr taaacaaatt gtratatattg tatgcaatat 300
aacaccactc agtaatatga aaatgaacta ctgatgtttg caaacggtg aaattcaaaa 360
taattatgct gagtgacaga atccagacca caaataatac ataatgtwtt attctattta 420
cataaagttt tagaaaaatc caaactaatc ttartttacc aaagccatac caatggtata 480
tggggcttgg ggcagkttaa acsgattatt gaaaaaaaaa attt 524
```

&lt;210&gt; 139

&lt;211&gt; 869

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 139

```
ctgattcctc ctcacatatg aaaagtgaag gttgtgagtt gttttcctct tatttaaaca 60
ttggcctatt ataactctgt ttggttattt ttctcctgta agcatcctga tttttctgta 120
ggaacttttc tttaaatgac acacattgcc acttgtgtag atatttttaa gttctttggc 180
taagtcctct cctaactgcc tgtcctctgg ttagggccct cctctccac tagtgggtgaa 240
tgcatgtgtc tgtctgatca gcatcactgc acacggaggt ctagtgagcc tcttgctaag 300
tgtcacacac actcttccca aagacgtgat gagttaaggt tgtattctga aatcatgaag 360
ccagagcctg tgccagacct tctgctacct ctcatagaat tgctctgtaa ttctaaattt 420
aaaattagaa gtagagagag ataagccatc gcccctttgc ctctgagaat tggctgctgt 480
ttctaataata attattttct aagatagcca gatagttaga aaaagatttt cattgatgac 540
atatctttaa actttcttgc atcagtattc taaattgagc aaactgaaag attttcatca 600
```

79

```

ggaaaggagc actgtgggaa gagcccagta ttcacatttt ttccccattt ttcagaagcg 660
acatttcata tataggtgcc aaaagtgaat cggggtgctg agagtgggaa ccttttgaat 720
ttatgattgt cacagagatg gtagaaatta tgatctgact ggaaaacaat cctgtatccc 780
ctcccaaaga atcatgggct ttttttttga attaaaaagc agacaaatag actttctcgg 840
gaaaaaaaaa aaaaaaaaaa cgcggccgc 869

```

```

<210> 140
<211> 586
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (5)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (439)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (563)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (577)
<223> n equals a,t,g, or c

```

```

<400> 140
ggggnaccag cgcgggtgct cagacgaaag gcgctctttg ccagctgaaa gttcccacgg 60
aaaaactacc atctcccctg cccaccatgg cagacgaaat tgatttcact actggagatg 120
ccggggcttc cagcaattac cctatgcagt gctcggcctt gcgcaaaaac ggcttcgtgg 180
tgctcaaagg acgaccatgc aaaatagtgg agatgtcaac ttccaaaact ggaaagcatg 240
gtcatgccaa ggttcacctt gttggaattg atattttcac gggcaaaaaa tatgaagata 300
tttgtccttc tactcacaac atggatgttc caaatattaa gagaaatgat tatcaactga 360
tatgcattca agatgggttac ctttcccctg tgacagaaac tggatgaagt cgtgaggatc 420
ttaaactgcc agaagggtgna actaggcaaa ggaaatagag ggaaaataca atgcagggtg 480
aagatgtaca ggtgtctgtg catgtgtgca atgagtggaa gaatatggct gtagccataa 540
aaaccctgtc aaataaaaac ggnaacattc aggccangga ccactg 586

```

```

<210> 141
<211> 614
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (546)

```

<223> n equals a,t,g, or c

<400> 141

```

aaataaaaag gcagtggccc caccacattt ttttcagcat agtagctggc attttgttat 60
cattagccag agtagcttca gcatataagt tattgatgtt ttccaacttc aaaagtgcac 120
tttatcctcc cagtaaattt gataatgatt tgtcacagct ttgtcatctt ttgacttttg 180
cttatgggcc tcacttcgta caactataac atgaaaaagg attgtcctaa agtaagggaa 240
tcagttaatg gtaggatgaa gaaactgtaa aaactcctag aaaaaaaacc tgtgtgcatt 300
tttctggaaa gttttcaaac tgtgtaattc agttttcatt caattatata atttggttat 360
atgcttttaa aaacatttgt ctaaagtgtc ccggttttct tctggcttta gagtcagctg 420
agtgtctggc atgcagccac tcgtattttt gcatccagaa aggagtaact ccctttatat 480
gaagrttttt tttttaagct tagatgctat gtaaggagaa aactatttgt aatcacatag 540
taccnngggr ggggagtgrr ggatgctttt ttaaaaaagg rtatttaagt atattatgta 600
atttaaatat aaat 614

```

<210> 142

<211> 574

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (19)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (522)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (574)

<223> n equals a,t,g, or c

<400> 142

```

ntgttaagtt ctgacattng gagaaaatac attacaaaga acaggagctg gtttttggtt 60
ttccttggtg ctgtgttttt gaattgaagg gatgtgggat ggtggtgaca gaagtctgag 120
catagtttct gaataattgg aggggagatg ggcattcttt gggactatgt ccgcattaca 180
ttgagttttc tccctctagg aagagagagt ttgtgtttta ttttctgtaa gtaaaagcta 240
catgttttag atttttaaac catattaatt gttatatttt gtatttcata attatattat 300
gtgttagtgt gtactggaat aacatgtttt atttggttag ttggtgcaaa agttttctaa 360
atctactgct gtattagaaa ctgaaaaggg agggaaattc cagatgtttg atgggaacat 420
cactggtgaa tatctaggrt tggtaaagtag acycaagggt gaagragtaa ggtgggggta 480
acccttaata ttaccttkgg tatatgcccg tttttagcac cngaatacag ggggtccttt 540
gttccccaac cttaacagca gccctgtctt ggtt 574

```



<210> 143  
 <211> 2012  
 <212> DNA  
 <213> Homo sapiens

<400> 143  
 tatgcaagct cgaaattaac cctcactaaa gggaacaaaa gctggagctc caccgcggtg 60  
 gcgggccgctc tagaactagt ggatcccccg ggctgcagga attcggcacg agtgtagagc 120  
 tcaaagaaat ctgccaacat gtatgtggac tcttgagagg tgggctttcc cagtacatgc 180  
 taaacagact tgttatgcca agaggaagtg aatagaaatg atagcatcaa atatccaaac 240  
 tgacaggaag tttcttttgc atagcataga acatggttgt cttctgagtt ccactaatgt 300  
 tccaggatat cttggccctc tgcctctggc tgctccctgg tgtttggcac catagcggtg 360  
 tcacttacaa ccattgcctt gggacacaca gagtgaactg tttgagtgat aagtaattta 420  
 ggtagaaact ttacccttaa tttcaaataa taccaaacag ctcaattacta cccaaggga 480  
 cgctctccgt agcttctgga ttccccagtt tccttctaga aacaaggact ccaatagcac 540  
 tataacccta aacaggccct aaccagaaag aatacaccac aaaatgcgat tgattttctc 600  
 aaaatatcac agtcttagac actatacaaa taattcaaga aaattctttc taccctgcag 660  
 tggatatagt attctattat attctccagc aaaactttta ggacttttca aactcatttc 720  
 taagccaaat agtttagata aatatattacc cttatatttg gggggaattc aggctcacca 780  
 tttgccgagg caagcccatc aacagtctag aggcatattc tgtgtcattc cttcccgtct 840  
 ccttcataga atactacttt ttctttttgt ctcttgcca ttctccatca tctgctgatt 900  
 attgctaacc acaggatgct ggcaaagctt acagtgatag gcacatgtgt tcagtgatgt 960  
 ccaatacact cttatcacag tggttattgc ttcttactct tttcaaagtc attattctac 1020  
 ccctcaacct atatccaatc attagaacta tacctgactg gagcccagaa cttgggacca 1080  
 atacttaatt caaatagcag gggcttgctc acaaacatta agcccaaaaa gaagcacagc 1140  
 actttgaaaa gtcaaataag cctttggtag ctctgtacat ttgcaatttt acatttggtta 1200  
 ttagttttata gcaactaata cacttcagtc gtgaatctac agtctcaata tgataagtct 1260  
 tagaacatgt tctagaaata gtggtacctt gctgctatta tacttagtaa cttatacccc 1320  
 aatataataa taagtattaa atacagattg tgtatgcatt ctttgtgtgt atatgccaac 1380  
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 taataataaa gtataccaat ttaaggtta gaattaaaat tttgcacata tgcttcttga 1620  
 tattctgaaa tgtattctgt ggcttaatta tcttattcat acacatttca ctttggcttt 1680  
 ttacccttag gaaataactg tccaagtata tatctcgtct tcttcttgt aactttgatt 1740  
 aaactgctta cttcaactta caacattgta aagccagaat acctcatttt aacagtgaaa 1800  
 aaaaatatga tgacctgatg tgttctcttg tatttgattt gaactaccta aataggctta 1860  
 actgtaataa taaatataca attttggcag gcattttttc ctttgtttgg atgaacattt 1920  
 tgttatttgt ccacttctaa ttttgtctta aagagttata aactcagtgt caataaaaca 1980  
 tcttgttata taaaaaaaaa aaaaaaaaaa aa 2012

<210> 144  
 <211> 558  
 <212> DNA  
 <213> Homo sapiens

<400> 144  
 aagttttttc ttaccccatc ctagtgagtt tgaaagtggg cctgaccaga atgtctcttt 60  
 cccattttgc cccgtttgaa ttaaataataa tgtctactct ttaaaggctg aaggggtggg 120  
 tgaggggatt gtttctcatt ttgtctccca agtcattttt ctgctgtgaa atatgaccag 180

## 82

```

gcttgtagga agactcatct tggagaaaat gtgaagtaat caaattgctt gagattagtc 240
tcctattgta tattagagcc aaaacacatr ataactttgg caacagggag ttgtctagac 300
tcaattttca gaggtcccat tgtagtgagt taatattgct aatcatgtca atcacttgac 360
akggaagtca gtggcaaadc tttaaagtat gcatttgata ctggcaaata tatactactg 420
atgtttcaca aaagaatctt agaatctgta gaaaacatta attacttcca tgaattattt 480
ctaaagtata acttttaaagt tttgattttt ctattttaat aaaaagcyat kgatgkgttt 540
agcakgtccc caaataga                                     558

```

&lt;210&gt; 145

&lt;211&gt; 1026

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (182)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1007)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1014)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 145

```

gcatttatat cctgttaagc attaatagct aatcactggg acttgaattc tgatggcaga 60
tagtctcttg cttagtgaga tggagttaac tatttttttag taggaagtga gaacagctga 120
ttttcatgcc acgtttcata gcccactttt tggtagacta ccaccacgct kcttcgcgta 180
anagtyggca tcttgggaat gaatgccagc ccgctcgtgg gttggtgcaa agaagtataa 240
acatatatca ctaaggaaaa agaaagtttg tcttgccctt ctgacacagt gtgtgcactt 300
caggcaattt ttggaaaata taaaaaatlc caawttctgc ctttcagcag catcaattgc 360
taggaacatt tcattcattt ccctgtaata ttaatgttct ttaagcataa tcactaatta 420
taagtgtgat cctatttttt tccagcttaa tttctgtggg ttattgaaaa ccaagtataa 480
atgtgactaa aagcattttg ctttgttttt atagttaact ttcytaagggt tatggacatt 540
twataatgta acatttgatt ggccctggcc cttgacaatt cccttctagt tatgcatatc 600
ctccctgttg cccacatttc ttgtttttaa actcagtttc ttgttttcca gttgttgcta 660
tgtataacac ccattcttgaa agagagtata taggaagtta ttcagataac ttttgtagta 720
gtgatattca actatagcag taccttaact catgatgagc ttaggaacat aaaagataat 780
tgttgcttga atagcaccac cagagatact gacctaatgg gtctgggggtg gagatctggc 840
atggtagttt ttttcaagct ccaatcatcg gccagacagt tgctttatgt aggttttttaa 900
atgccaaagg cagatatgaa gtagatttaa ttaagacttg acttcagcaa tacaggggaa 960
cttaaaatac ttrtttttct ttaaactgca ggagtcactg ttaggtnttg cttnaaaaaa 1020
ttgcat                                     1026

```

&lt;210&gt; 146

&lt;211&gt; 521

&lt;212&gt; DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (440)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (474)

<223> n equals a,t,g, or c

<400> 146

```

gggacctggc aagcggcggc tgcagggcag gtccaggggc cacatggctg aggggggacgc 60
acggagcgac cagaggcaca atgaggaaat tgaagcaatg gcacccattt atggcgagga 120
gtggtgtgtc attgatgact gtgccaaaat attttgtatt agaattascg acgatwtwga 180
tgaccccmma tggacacttt gcttgcasgt gatgctgccs aatgaatacc caggtacagc 240
tccacctatc taccagttga atgctccttg gcttaaaggc caagaacgtg cggatttatc 300
aaatagcctt gaggaaatat atattcagaa tatcggtgaa agtattcttt acctgtgggt 360
ggaggaaaat aagagatggt cttattacaa aaatctccag gtgacagaac caggcccaga 420
tgttaaagga ggaaaactgn aggaggaaga tgttggaatg tggaagggtg atcnccattt 480
ttagcatggt cagccgggaa agttcgggtt aaaagcattg g 521

```

<210> 147

<211> 557

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (17)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (527)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (543)

<223> n equals a,t,g, or c

<400> 147

```

ggattaacca ttaaatngat tgaaaaggaa actttgcacg gtatgagctt cataccccca 60
ccaaacaaag tcttgaagggt atttatttta ccaagtatat ttttaaagtt gttttataag 120
agagactttg tagaagtgcc tagattttgc cagacttcat ccagcttgac aagattgaga 180
ggcccatgcc aacagtctaa tctaagagat tagtctttca aactcaccat ccagttgcct 240
gttacagaat aactcttctt aactaaaaac ctagtcaaac aaggaagctg taggtgagga 300
gatctgtata atattctaata ttaagtaagt ttgagtttag tcaactgcaa tttgactgtg 360
actttaatct aaattactat gtaaacaaaa agtagatagt ttcacttttt aaaaaatcca 420

```

## 84

```

ttactgtttt gcatttcaaa agttggatta aagggttgta actgactaca gcatggaaaa 480
aaatrgttct ttttaattctt tcacctttaa agcatatttt atgtctncaa aagtattaaa 540
aancttttaa tacaagt                                     557

```

&lt;210&gt; 148

&lt;211&gt; 1023

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 148

```

ggcacgagga accaccttct gtaggacagt caccaggcca gatccagaag gcttgaggcc 60
ctgtggtccc catccttggg agaagtcagc tccagcacca tgaagggcac cctcgttgct 120
ggtatcactg cagtgcctgt tgcagctgta gaatctctga gctgcgtgca gtgtaattca 180
tgggaaaaat cctgtgtcaa cagcattgcc tctgaatgtc cctcacatgc caacaccagc 240
tgtatcagct cctcagccag ctctctctta gagacaccag tcagattata ccagaatatg 300
ttctgctcag cggagaactg cagtgaggag acacacatta cagccttcac tgtccacgtg 360
tctgctgaag aacactttca ttttgtaagc cagtgcctgcc aaggaaagga atgcagcaac 420
accagcgatg ccctggaccc tcccctgaag aacgtgtcca gcaacgcaga gtgccttgc 480
tggtatgaat ctaatggaac ttctgtcat gggaagccct ggaaatgcta tgaagaagaa 540
cagtgtgtct ttctagttgc agaacttaag aatgacattg agtctaagag tctcgtgctg 600
aaaggctgtt ccaacgtcag taacgccacc tgtcagttcc tgtctggtga aaacaagact 660
cttgaggag tcacttttcg aaagtgtgag tgtgcaaattg taaacagctt aacccccacg 720
tctgcaccaa ccacttccca caacgtgggc tccaaagctt ccctctacct cttggccctt 780
gccagcctcc ttcttcgggg actgctgccc tgaggtcctg gggctgcact ttgccagca 840
ccccatttct gcttctctga ggtccagagc atcccctgcg gtgctgacac cctctttccc 900
tgctctgccc cgtttaactg cccagtaagt gggagtcaca ggtctccagg caatgccgac 960
agctgccttg ttcttcatta ttaaagcact ggttcattca ctgaaaaaaaa aaaaaaaaaa 1020
aaa                                             1023

```

&lt;210&gt; 149

&lt;211&gt; 1256

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 149

```

gctcagcctc ccaaagtgtc ggtattacag atgtgagcca ccgcacccag cctgagtttc 60
tctttctctc tttttaactt tattttttga aaaaccgggt agactttgtg gggagcattt 120
ttgttgataa ttactgatac taaagctgag tgatttttta aaagaatttg aatctaatag 180
atctgtggtt gaatttsctg tgttggtatg aagtccaccc tgtgggcaca ataacataac 240
tgttggtagg agttgtttga gctattctgg agattatttg gtaaagtata ctaaaagcct 300
taaaaccatg tatgtgcgct gtttgaacca gtaagccact tctttgacat tagaagacat 360
tagaagaaat aatcagcctt gcataaaaact tatggatgaa agtattcatc acaatattat 420
ttataataaa aaattgcaaa ttttataaat gaacaattgg gaaatgggta aagaagtgat 480
gggtgcattgt gtggtagaat attatgcata tgtttaaaga atcatatttt ctaagattat 540
ttggaagcat gtttggtaat gtcaagtggg gtaccccgag tacatttttag acatttatcg 600
tcatcatctg ctctgagtgg aaggccgttc agagaggcta gaggttctta ttctggctat 660
aaattatgtg agtaaaaattg tgctaaccag ttaaaagtac tgtacacca tgctcaatat 720
atagtcctgg aaatagcaat tgaacatgt cttctcaca gagaaaatga cagttttaat 780
gatgtatttg atgaatttaa actttaagtc aggtgctgca aattggaaag aagacttggt 840
gtgttttaag ttgctgtgga cacttttaag aaacttagaa ccatgggaac ccttgtttat 900
cgccatgcaa attacaatct tgaatgagtg ttttttaaaa ataaagtatt agaaaaatgt 960

```

## 85

```

gtagtaaaga tgtaaaatta aaaaatggaa ttctccatta actgtggatt ttactaaata 1020
gaattactgg tgaagcagat ttatccatcg agactatctg gtatgcgtta tgtatgtagt 1080
ctgttgctgc tgaaagatgt ctgtgtgcct gtatcaacat gtgacttcat gtaaagtttc 1140
tttgtgttca cagttcttag caaatgcagt tacaatccat agatagccag cagtggatgt 1200
tactccagga aaatgcagga ttaaaattgt ccttgtgtaa aaaaaaaaaa aaaaaa 1256

```

<210> 150

<211> 698

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (683)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (692)

<223> n equals a,t,g, or c

<400> 150

```

cctcgctcaa gccctcagag aagaacattt tcaccctctt catggtggcc acagctgcca 60
tctgcatacct gctcaacytc gtggagytca tctacctggy ragcaagaga tgccacgagt 120
gcctggcagc aaggaaagct caagccatgt gcacaggcca tcacccccac ggtaccacct 180
cttcctgcaa acaagacgac ctcccttcgg gtgacctcat ctttctgggc tcagacagtc 240
atcctcctct cttaccagac cgcccccgag accatgtgaa gaaaaccatc ttgtgagggg 300
ctgcctggac tgggtctggca gggtgggcct ggatggggag gctctagcat ctctcatagg 360
tgcaacctga gagtggggga gctaagccat gaggtagggg caggcaagag agaggattca 420
gacgctctgg gagccagttc ctagtcctca actccagcca cctgccccag ctcgacggca 480
ctgggccagt tccccctctg ctctgcagct cggtttcctt ttctagaatg gaaatagtga 540
ggccaatgcc cagggttgga gggaggaggg cgttcataga agaacacaca tgcgggcacc 600
ttcatcgtgt gtggccccact gtcagaactt aataaaaagtc aactcatttg ctggwaaaaa 660
aaaaaaaaaa aaaaaaaaaa ccnggggggg gnccggta 698

```

<210> 151

<211> 1710

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (142)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (208)

<223> n equals a,t,g, or c

<220>

<221> misc feature  
 <222> (242)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (317)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1644)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1707)  
 <223> n equals a,t,g, or c

<400> 151  
 aatttcggcc cgagggtgag ggcagctgga gtgcgttctg ccgaagcttg tggttgcacg 60  
 cccttcgtct taggggctac ctccgtggt gagtgtgtgc ggtggtgcac ttgggggttg 120  
 ttctcgtctg gtggccgcac gnggctgaac ccttccact ccatccctc cccgcacccg 180  
 gaccagcccc tgggacgccc tcggacgncc acccgtcca accctgggga agcctcagag 240  
 tngcagcgaa ggcctyttgc ctttccgcct ctgcgttgc tgtcatcgcc cacgtgcttt 300  
 gttgttgttc ggtgcanacc atgtccaagt ctctgaagaa gttggtggag gagagccggg 360  
 agaagaacca gcccagagtg gacatgagtg accggggcat ctccaacatg ctggatgtca 420  
 acggcctctt taccttatcc catatcacac aactggctct cagccataac aagctaacaa 480  
 tgggtgccacc gaacatcgca gaactgaaga atttggaggt gctcaacttt ttttaataacc 540  
 aaatcgagga gctgcccaca cagatcagta gccttcagaa actcaaacac ctgaaccttg 600  
 gcatgaacag gctgaacact ttgccacgag gcttcggctc cctgccagct cttgaggttc 660  
 tggacttgac ktacaacaac ttgagcgaaa attctcttcc tggaaaactt ttctacctga 720  
 ccaccctgcg tgcactctat ctaagtgaca acgattttga aatcctgccg ccagatattg 780  
 ggaagctcac aaagttagcag atactcagcc ttagggataa cgacctgatc tcgctgccta 840  
 aggaaatcgg ggagcttacc cagcttaaag agctccacat tcaggggaac cgcctcaccg 900  
 ttctgcccc agaactagga aacttggatt taactggcca gaagcaggta ttcaaagcag 960  
 agaacaatcc ctgggtgacc cccattgcag accagttcca gcttggcgtg tcccatgttt 1020  
 ttgagtatat ccgttctgag acatacaaat acctctacgg cagacacatg caggccaacc 1080  
 cagaaccacc gaagaagaat aatgacaaat cgaaaaagat cagccggaaa cccctggcag 1140  
 ccaagaacag ataaggaagg gattggcatc ggctggcctt ccagcacctt ctctctccaa 1200  
 cacttcattc tctcttgccc tgtctctcaa ataaacccaa tgcctgcgtg gaggcctttt 1260  
 ttatttttct tttcactctc tttctaattgc tttccacctt accttttaga ttcttttgc 1320  
 aggtgggaga ttgttataag gtcttttaaac catttccatt tgtttcttta acattaccaa 1380  
 aagcagggaa caaagctctt attcaactgc gaattccata gtgggctctg gcttttcttg 1440  
 aatagatatc acaaggttgc ttattatcaa aagaataatt aaaatcatgt aaccatttaa 1500  
 atgtcactgt taacactttt cactctttct gttgattcac ctaactcatt attttgcttt 1560  
 attaaaagtc ttcttcacc accgagatat gctaatttaa cttacaaatg attttaataa 1620  
 aatcttgagt ttgtaaaaaa aaanaaaaaa aactcgagag tacttctaga acggccgcgg 1680  
 ggccatcgat tttccaaccg ggtgggnacc 1710

<210> 152

&lt;211&gt; 1121

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (532)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 152

```

ggcacgagggc agaatggtcc tgccagccac agcagggccc tgggtggggat ttgcaactggg 60
cactccaatc ctggagagga tgccagggac ggggatgctg aggaagtcag agagcttggg 120
acggttgaag aaaactgagt cttggggcaat ttgtgctaaa actaggtgag ttgccaaacc 180
caaggcatct taccaacagc tggtttgggg gctgggttcc ctgggtgtgt gtgttaccta 240
ccctttggct tggcttgacc tctccttggt agctcacctg agccctccca gggccagggt 300
cctgacagtg ttggtttttg cacatccact ggaaagggtg cattaatgac ccagtgttag 360
aatgcaagag gtcagggttat tctagccctc atggctgaag gcccagtcct ggctccacca 420
ctcctccagc cagaggggtc ggaccatcca gtgcctgtcc tcgccacagg gcctccaggg 480
agcattcggg tcaawtccat ggacaccctg ggctacaaac caaggctgct gntcatcca 540
catcgtgtgg ggcagtgtcc atccccctga gctacttggg gacttaacaa ctycaggagc 600
cctgtcagct gccctcctcc acctaaaccc ctctgactct tctgctttga caaagaaaat 660
gacattgggg aggggaggtg ctccgcctcc cagcttttct caaaatagtc ctatagatac 720
tggtaatctg gaaatgaaga agtaattctg tctctgcacc tacttttgca gaatgttcaa 780
ggaagtattc tgtgttagta ttaatgcaa aaagtgtgtt ttaaagggtt tgtactcagc 840
acatcataca aaccacatta cttctgtcac ttcagggcat cgggactggc tggcgccctt 900
gttatgtgct attttaatca gtgtaacatt ggtcaagttg ttacccatgt atgctgtgtt 960
tatcatgtgt atatcgtcya gaaagtatta aggcttttag tagatgcaac tggcgaaacct 1020
tggagagggg atgctgattg tcttgaccaa acccacagcc tgtctcttct cttgttttagt 1080
tacttacggc aataaatcat ctatgagtta gtgcaccgtg a 1121

```

&lt;210&gt; 153

&lt;211&gt; 445

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (440)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 153

```

ttttcttgca tctgcccgcg atctttctcc agacctttct gcgagtacga gccaaaccggc 60
agacccgact gaatgctcgg attgggaaaa tgaaacggag gaagcaagat gaagggcaga 120
gggaaggctc ctgcatggct gaggatgatg ctgtggacat cgagcatgag aacaacaacc 180
gctttgagga gtatgagtgg tgtggacaga agcggatacg ggccaccact ctctggaag 240
gtggyttccg aggcctctggc ttcacatgt gcagcggcaa agagaacccg gacagtgatg 300
ctgacttgga tgtggatggg gatgacactc tggagtatgg ggaagccaca atacacagag 360
gctgatgttc atccccctga caggcgagga gctggttgaa gccaaaggaga gagaggcatt 420
tcggggcgca ttcttaaatn gccgg

```

&lt;210&gt; 154

<211> 798

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (638)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (665)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (698)

<223> n equals a,t,g, or c

<400> 154

```

agctcttaga caggtacaga gaactacaac ttagtacaga aagcaaagta acagaatttc 60
tccatcaaag taaattaaaa tcttttgaaa gtgagcgtgt tcaacttctg caagaggaaa 120
cagcaagaaa tctcacacag tgtcaattgg aatgtgaaaa atatcagaaa aaattggagg 180
ttttaaccaa agaattttat rgtctccaag cctcttctga aaaacgcatt actgaacttc 240
aagcacagaa ctcagagcat caagcaaggc tagacattta tgagaaactg gaaaaagagc 300
ttgatgaaat aataatgcaa actgcagaaa ttgaaaatga agatgaggct gaaaggggtc 360
ttttttccta cggctatggt gctaattgtc ccacaacagc caaaagacga ctaaagcaaa 420
gtgttcactt ggcaagaaga gtgcttcaat tagaaaaaca aaactcgtctg attttaaaag 480
atctggaaca tcgaaaggac caagtaacac agctttcacm agagcttgac agagccaatt 540
cgctattaaa ccagactcaa cagccttaca ggtatctcat tgaatcagtg cgtcagagag 600
attctaagat tgattcactg acggaatcta ttgcacanct tggagaaagg atgtcagcaa 660
cttanaataa agaaaagtca gctttactac agacggangg aatcaaaatg gcattaggat 720
ttaggaccaa cttctaaatc atccgtgaag gaaatttggc aagcaaataa aaaccagatt 780
cctcggttaa gatgcatt                                     798

```

<210> 155

<211> 400

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (74)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (379)

<223> n equals a,t,g, or c

<220>



<221> misc feature  
 <222> (383)  
 <223> n equals a,t,g, or c

<400> 155  
 ggaatctgga agcctgactt tgccccagc gaagttgggg accgccttcc ctcccttctc 60  
 cacctctcac tctnggcacc ctctccaatt gcactaaagt agctgttggt ccagtctgcc 120  
 cccacaagg ggggaggtct ctgcttycag tcttcttccc ccgctgcctc cgctmccacc 180  
 ctggacaatc tccttgtttc ccttggtgtc mtggayagct cagctttgta tgtgtgtttg 240  
 ggggggtgggg gtgggttctg gcttgagtgg gtttggcagg gggttgggaa gggtagggg 300  
 aggatggagg atgaagtctc ctacccctt ctccagctcc aggccacaga agcctgggaa 360  
 agggaggggtg cctactctng gtngctagtg tgtctttgca 400

<210> 156  
 <211> 1757  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (596)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (647)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (648)  
 <223> n equals a,t,g, or c

<400> 156  
 gccagccacc attttatctc tctaaagtct ggtcccagta ttaaacctat tctttagtaa 60  
 actcatatta ctgttctaaa ttgaagaaat tattttattac tctgtacttc tagactcaaa 120  
 attctttatc aaagatagtc tcaaagaggt agtacaagtc ctgtttaact gcacttttct 180  
 acattcacag tgcttctctc gatattcttc cttacatcat tatacactgt tgatatcatt 240  
 ttactcttct ttctcttcta catttcttaa attttgggtc ttttcctgta catgtgtttt 300  
 agcggggccc ttttctttga actttgtcta attagcctgt acatttttgt ttcttttaag 360  
 gtagaacaga tctttttttg tttctccttt taagtctact ggtttttaaaa gaggtaaatg 420  
 tatccataga ccacagtgcc ttgctttttc ctctgccagc acatggagca cgggattaga 480  
 tgcacaaacc tatttaggga actatttttg tagatgtttg agtttataca gaaattgcag 540  
 ctggtatttt attttgctgt acatttactc aacttgcca ttagtattta actatntcca 600  
 gagtttgttt aggagtaaga attgacctat tegttagttt accatanntt ttcttggtat 660  
 aaaaaggagc cagaaataag ccttattgct aaataattaa ttatgtaagc ccacctaggt 720  
 cctgcataag atccccctca catacttcac aatatatatg tgtgtgtgtg tgtgtgtgtg 780  
 tgtgtgtgtg tgtgtgtgtg tgtgtatktg gctaaaaaat tatactgcca aaattactga 840  
 ttataaatac ttgactacac tgattgatgg gacaaaatga ttaaagtatt ttcagggatc 900  
 ttattccata tgtcaccacc aaagatttct acagtgttat aaagtatata aatattccaa 960  
 atttctgtgg ttaaataatt ttttcttttt tttccttttt tagaataaca cagtctgtgc 1020

## 90

```

tttccaaaaa tgcttgaact tttatgttgt taagaaatat ataatgatat cttacattaa 1080
gcatgagtct aatttgtatt aattgggatg gactaaatct tcatttgatt atcaggaaaa 1140
ttaaggagtt atatatttaa aagcaatctt ctgtgttttc ttctttgtaa gttgactcat 1200
ttgtgaagca attaggcaaa ttttgagaag atcattgtta ttgtgggttg cagtatatat 1260
ttcttagtaa atatcactta agattaaatt tttcagaaag aaaattatag cttttttccc 1320
aaaatatttt taagatttaa tctttttgta gtatgtaca gatttaatta tattaactct 1380
tttttaagac attgaccatg acttaacatt ttgccttcta acacctttta aatctatgta 1440
ctttaatagt taagagaaaa taagtgtgca gatttttaat aatctgtttg taaaaggcta 1500
tctctaagcc tagtatgtgg gtaattttac aggtgtgttt tttgataact ttaataataa 1560
ataaactcat tttatttgtg gcaattcgcg tttctttttt tatgccagag tacatatgtt 1620
ggattccatg aattgggtatt acttattatt atgtgttgat taaatatatg cacacactta 1680
ggattacaga tcacagagca aattatgaaa atcataaaca ttctggtatg gtcattccata 1740
ggattatgaa aaagaaa                                     1757

```

&lt;210&gt; 157

&lt;211&gt; 1245

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1245)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 157

```

gaaagccctg aatgttgtac aaagtgtttt gcaaataaac ttaagcaatt ctacaaacag 60
aggatcagta gctgctaaga aatttaagga catcatacat tatgatccaa cgaagcaaga 120
ccatgccact tacgaaagaa aaagagatga taagccaaaa gaaagtaaag caaacgaaa 180
aaagaaaagg gaggaagctg agaaactacc tgagggtgtct aaagaaatgt attataatat 240
tgctatggat ctgaaagaaa tattccaaac tacaaaatat accagtgaag aggaagaggg 300
cacaccctgg aatgaggact gtggttaaaga gaaacctgag gaaatccagg accctgcagc 360
tctgaccagt gacgctgagc agcccagcgg gttcacgttc tctttttttg attcagacac 420
taaagacata aaggaagaga cctacagagt tgaaacagtg aaacctggaa agattgtctg 480
gcaggaagac cctcgtttac aagacagcag ttcagaagar gaagatgtta ctgaagaaac 540
agatcacaga aactccagtc ctggagaagc atcattactt gagaaagaga ccactagatt 600
tttctttttc tctaagaatg atgaacgact tcaaggttct gacttattct ggagaggagt 660
aggaagtaat atgagcagga actcctggga ggccagaaca accaacctgc gtatggattg 720
tcgaaagaaa cataaagacg caaaaaggaa aatgaaacca aaataataaa tgtcagctgg 780
ttttgatact gaatgtgaac aaggctcacc taaggaaaact gaccagaaa acagtttttag 840
ctgacaaaaga agaaatttca gagtgaagga attttaaaaa tctggctgac ggaatatcat 900
tctggttgcc atctttttct gtggaactcc tctgcatttc ttctaagta attacttcaa 960
aaattaaatt caacttctta taaaggaaga acaagatagt ccttgaaaat actttttgta 1020
tataatctct ttgcctcta tcctgagtaa ctaatggaca tcttctcatg caaggtttay 1080
atgaagcctt tttwaataaa tgagtcaaag cacttgtatt ttccagccta ggctttgtgt 1140
gaattatagg ctatttgaaa ttttatttct gattatgtca aatacacctt ccgattttgt 1200
catttttgtt taaactgata aattacaagt caacattgag ttttn                                     1245

```

&lt;210&gt; 158

&lt;211&gt; 379

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

<220>

<221> misc feature

<222> (375)

<223> n equals a,t,g, or c

<400> 158

```
gtgagctgag accatgccac tgtactccag cctgggcaat agagcgagat tctgtctccc 60
aaaaaaaaaca aaaaacaaca acaaaacttg ctaccaccca gggattttct gctattttaa 120
aggtgaattt cttttctggt actaaactgt agctgcttaa cttagtaaag gctgtgtttg 180
gccaggcctg tgccagaggt cacctggagt gctccaccca ctggcaggca agtcctattc 240
ctattcaccc aggatcccca aggctgggct gggatataaa tgttgggata ggaaagaaat 300
atttcctttt tagaggaaaag caagaagaaa cattgcctga aagtgattty ctagtcattt 360
ccattagtagt agaangtta                                     379
```

<210> 159

<211> 474

<212> DNA

<213> Homo sapiens

<400> 159

```
ctttatcata ttttacaat gtgtgagtct gctatggatt agaaattaat aagagatttk 60
gccacagata gtttgagaag ccagcactg ccactcaaca aatgctggtg cattcagatg 120
gtgaaatatt ctgcagctat taaaggagtt aaaactgcct ccacttacct ggaggcccat 180
ctgtgacacc tttttagggtt aaaaggaaaa gaaaaacttg cttaggactg aatatgagcg 240
gttgcaattt gtaacaatga tgtatatata catatacatt ttcattgtatt tgtatgaaca 300
taaaagtatt gaaggatatt catcaaactg ctaaaagggt tgcttcagag taacggactc 360
ggagaaggca gattaatttt ctcttaatgg aactctgtat tgtatcactt gtaaaaaataa 420
gcatgtgtta tctttatgat aaaaaagtaa aaacctaaaa aaaaaaaaaa aaac 474
```

<210> 160

<211> 1444

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (4)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (5)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1373)

<223> n equals a,t,g, or c

<220>

<221> misc feature  
 <222> (1425)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1430)  
 <223> n equals a,t,g, or c

<400> 160  
 gggnnntagac accttagaga ttcagcagca agccctgcta agagagcagc agaagaggct 60  
 gaacagaata aaaatgcagg aaggtgccaa agttgactta gatgccatcc caagtgctaa 120  
 agtacgagag caaagaatgc ccagagatga cactagtgat ttcttgaaaa actcattatt 180  
 ggaatctgat agtgctttta ttggggctta cggtgagaca tatcctgcca ttgaagatga 240  
 cgtcctccct ccaccatcac agttgccctc tgcacgggag cgcaggagga acaaattggaa 300  
 aggactagac attgatagca gtcgtcctaa tgtagcacca gatggtctct ctctaaaatc 360  
 tatatccagt gtaaagtgtg atgagcttag agtgagaaat gaggaacgaa tgcgaagact 420  
 gaatgaattt cacaataaac ctattaatac agatgatgag agttcactgg ttgaccctga 480  
 tgacatcatg aaacacatag gggatgacgg atcaaaactct gtagcaactg agccctggct 540  
 ccgccctggc acttcagaaa cgctgaaacg tttcatggca gagcagctga accaggagca 600  
 gcagcagatt cctggaaaac caggcacttt cacttggcag ggcctgtcga ctgcacatgg 660  
 ttaaaataaaa cctgtactgg acccagtagt gccttttaag gtgaaaggaa tggtaaattct 720  
 gtacctttta tatgtcctac ttttggcccc tacctgaaag ttactttttt tccatcatct 780  
 gtatataaaa ttatttttat catgatgtat attatgtaca taaataaaaag gccatgatta 840  
 ttgatttata taatagaatt gtatagatta tttttgcaca gttttgtcat aaattagggc 900  
 ggtaatgaac tggattgaac tactatatgt gcattatatt gaattctgct tgtcattaag 960  
 ataaggtgaa taagtgtctt aaacgtcctg taaaaccgga ctcccctttg ttacatgcac 1020  
 attttccatt gttacctcga tgcaaaagaa ttcatttagt aggtacatct attgtagctg 1080  
 tgattattcc agtttctgtg tgatgcaatc aaatgtccta ttaattaatt attatttcat 1140  
 gtcatttgta gctactgata cagcagaaat gaaggggaact gtaattactt gtatttttgt 1200  
 aagccatacg ttaaattgtt gttacatcat ctttctgctt ctatttttat gccaatgaag 1260  
 gcatttgtct tgttactaat tacatgatgt aactacttct tgatataaat aaatttttat 1320  
 tttaattact aaaatctttt taactactat ggagctttct agactagttt tcnagagggt 1380  
 gaatagaggt ggggacaccc ggggagtcaa ggacagagga gactnggagn cttccttctt 1440  
 ccca 1444

<210> 161  
 <211> 449  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (268)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (269)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (368)  
 <223> n equals a,t,g, or c

<400> 161  
 aattcggcac gagttggaat gtgagatggt ggttgagagt caggatctct tttaaaagtg 60  
 atcttgagca agttatttaa acttttctaata tctcagtttc tttatctgta aaatggaggt 120  
 aatgggaata cttacctcaa attgctgaga gaattaaatg aaataattct gcaagatagt 180  
 tatcacagta aagcagtaaa tgctccattc aggggtaccat tactattgac tgccttaaaa 240  
 atttaattctt ctagccagggt gcgaaaannc atgcttgtaa tctcaacact tttggaggcc 300  
 gaggtgagat gatcatcttg agcccagagag ttcaaggatt aaccagagta acatagcagg 360  
 gatcttgnt ctattttttt aaaaaagtca ccttgtaaca ctggtgaatt ggataaggag 420  
 caattcagat gtagecgaatt ttaataatg 449

<210> 162  
 <211> 573  
 <212> DNA  
 <213> Homo sapiens

<400> 162  
 cccaccctga aagccctgag ctttctgcta tcaaagaggt tttaaaaaaa tcccatttaa 60  
 aaaaaatccc ttacctcggt gccttccctct ttttatttag ttccttgagt tgattcagct 120  
 ctgcaagaat tgaagcagga ctaaagtctt agttgtaaca ccatgattaa ccacttcagc 180  
 tgacttttct gtccgagctt tgaaaattca gtggtgtag tggttacca gttagctctc 240  
 aagttatcag ggtattccag agtggggata tgatttaaata cagccgtgta accatggacc 300  
 caaaatttac cagaccacaa aacttttcta atactctacc ctcttagaaa aaccaccacc 360  
 atcaccagac aggtgcgaaa ggatgaaagt gaccatgttt tggttacggt tttccagggt 420  
 taagctgtta ctgtcttcag taagccgtga ttttcattgc tgggcttgct ttagatctt 480  
 aggaccwat gctgcttgag rcaactcatc ttaggggtggc aaaaaggcag grtggccggg 540  
 cgcgtggtca mgsetgtaat cctagcactt ggg 573

<210> 163  
 <211> 1037  
 <212> DNA  
 <213> Homo sapiens

<400> 163  
 aattcggcac gagctgtctg cgaagtggcc cttgattaca aaaagaagaa acacacctaa 60  
 acactttatc tccaagttac aaaagtgtga ggtgcagagg gaaggccaga tttttttttt 120  
 aatgaaatta tatagattag atctcagtat ttaaactggt cctcaatttt gtgaggctgt 180  
 gttggaaata acccgccctct agtgctgttg gtatgcaagg cagcgggtgct taatcaatat 240  
 ttctgtgtgt caccagaggc aaaatgtacc aatatactga caccattctc tctccattta 300  
 cttctggttg ttaccttgac tcttgactct tagaagtgcc cgagatgggg ctaaccttta 360  
 ttaaacagat cgcataattat gatcttgctg cagccacagt gcagctccac attaatctta 420  
 cagaccaaac catttgatc tggcatcact tactaacaca cgacatgcgg cttttctgca 480  
 tcaactgcta tgacggttaa gaatgtcagt atacaagaag gaatagaaaa ctgatactgt 540  
 tttaaataat ctgtaatttc aatttttttt tttttttgct gaaatacatt atattgtacg 600  
 tttgagataa ttctagtaca aagtataata aaactagatg tataataaac cttttaaatc 660  
 attggtaagt gtacaagtgg tggaaactgaa gcatttactg gacaaagtaa tgttactcta 720  
 atggttactt gctcgtgctg tgccacactg tggtataatt tgcttcattt ccttgctatt 780

## 94

```

tgatacatag tgtgcatttc tctgtcactg taactattgt aatgacaaat tttcatctta 840
ctgcacaatc aaaatgacat tgataggaat gaactccaga ggctgggcct gaacagggag 900
gtggtcgctc aggcctggtg ctcagtcgta cgacctgtac ctctcaactt ttgccctatc 960
tgttaaatat atgctatgtc attaaatgct tttaaatcta aaaaaaaaaa aaaaaaaaaa 1020
aacggggggg ggccccgg                                     1037

```

&lt;210&gt; 164

&lt;211&gt; 921

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (881)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (908)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (913)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 164

```

ccccccccc ccttgtggac agctgtgtta ataaggccaa ttttctgaga atgtgggaaa 60
gattaaaaata tttaactggt tatctttcac agagtagcag tagctctgat taagcctata 120
ggcaattaaa agtagtttgt ctgtaaaaag agggaaagaa ataagatttc ttacccatt 180
ttatggactt ttaaaaatta aaaaactgcg cccccgccca ggagctcttt tcttatgaca 240
tataaattat gacatttata ttctttatat gactttatgt tctcttctta tgacatttaa 300
attctttaag tagtttgttg gtccaataaa ctagacgttg tataatctaa attgagccct 360
tgtatatcta aaactgatga gttgtttcta aattgttgat tgtccattta cttgcctttg 420
gtattaagat aatgcaagta aagtttagta agtcattgga taatgaaatg attatgtttc 480
tgaagaccat attatatatt taatttttag aggaatcatg ccatcccca aaaaatcaag 540
aaatatttga attttaaatt ataagttcat ttgttaaaag acatttttac aaatgtctga 600
aaatcttaaa atactttaca tctacctta agtagtagaa tacagagctg taaatttcca 660
tgcctttttt cctgatatta agttttatag taataaaagca actagtgatt gcacaaagaa 720
tataaaaaatc caytcttttt acaaagggtg gaatttaaata aacgttattg attggaatat 780
gaaaataaac caatcattta agagcttttt agcaaatgat ccaattctta ctccttttct 840
ccaagattg gaaaagcata atgtttttcc tcctaaagtt nggaatccta gaaaagcccc 900
ggtgagtnng acnaatgttc c                                     921

```

&lt;210&gt; 165

&lt;211&gt; 465

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

<222> (428)

<223> n equals a,t,g, or c

<400> 165

```
aattcggcct cacagagatc atcatcttta ccaccttcaa atcgtaaadc aagtactcca 60
aaaaaaaaactt attctgagaa agccaccgat aacctatgta atcatagctc ttgccctgaa 120
ccggtgccaa atggagttaa gaaagtatct gtgagaacag cctgggagaa gaataaatca 180
gtagctatg aacagtgtaa gccggtttca gtcactccac aggggaatga ttttgaatat 240
acagcaaaaaa ttcggaccct agctgaaaca gaacgatttt ttgatgaact tacaaaagaa 300
aaggaccaga ttgaggcagc actaagcagg atgccttctc ctggaggacg ratcacttta 360
cagamraggt taaatcagga agccttggaa gatcgtttgg aaggattaat cgagaactgg 420
ggttcagntc gcatgacgct aaagaattcc atgttttgcg cacct 465
```

<210> 166

<211> 752

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (651)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (662)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (684)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (693)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (700)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (711)

<223> n equals a,t,g, or c

<400> 166

```
gtggaaactt tttccatcct gttttctctg ctatatctgt cagcccccat ytccaccwac 60
atcagagaag acagcatcgt gaagcttctg tggcagcctc ctaaggaagg ggctgccaat 120
```

## 96

```

ctgtagttgg cagatgctat aggaattgct tacaaatgtc gtctttaaga aaaatgttct 180
tatatttttc ctatgggcaa aatgaaggct tgggtgctca tctaaagctc agccaactcc 240
tgaagcactc tctcagagca tactgctgct gtaatgggct ggcttaatta tcggcagagt 300
gcttgaaaag gctttgcaga cctcccctgc ccccaagact gggtgacttt atatgtactt 360
cattcaaggg taaatcaggg agacgttctc catttatctc ttcgtccttc ctgcctggga 420
aagtgatagc actaaatatt tcccagcagg atggggtagt gtttctcaaa ggaatcacc 480
tttccctacc ttcagactca ttctttaccc ttccattgst ccagtgtga tggaggccaa 540
agacaacccc agggttttca taggaaattc actggaattg tgcgcaattg tctttgtagt 600
ccttttgctt tttttttttt taaatattta tgttggcaat agcatttggt ngggatattt 660
gntttaaaag gcctcactct aagntattac cgnccccttn attgggtttt naaagacatg 720
tgggggggata tagtttttaa aaaataaacg ta 752

```

&lt;210&gt; 167

&lt;211&gt; 1631

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (255)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1620)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1630)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1631)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 167

```

tccagagatg tttcctgtcc tccccgggtc ccacttgctg ytcaataacc ctgccctgga 60
gttcatcaaa tacgtgtgca aggtgctgtm cctggacacc aacatcacia accagggtgaa 120
taagctgaac cgagacctgc ttgcctggt ggatgtcggc gagttctccg aggaggccca 180
gttccgagac cctgccgt cctacgtgct tctgaggtc atctgccgca gctgtaactt 240
ctgccgcgac ctggnacctg tgtaaagact cttccttctc agaggatggg gcgggtcctgc 300
ctcagtggct ctgctccaac tgtcaggcgc cctacgactc ctctgccatc gagatgacgc 360
tggtggaagt tctacagaag aagctgatgg ccttcaccct gcaggacctg gtctgcctga 420
agtgccgcgg ggtgaaggag accagcatgc ctgtgtactg cagctgcgcg ggagacttcg 480
ccctsaccat ccacaccag gtcttcatgg aacagatcgg aatattccgg aacattgccc 540
agcactacgg catgtcgtac ctctggaga cctggagtg gctgctgcag aagaaccac 600
agctgggcca ttagccagcc ccgggccccg ggtgcctctg cgtecggtgc aggcctcctg 660
atgccaaggc cacatccccg tgcttccagt gaccagacca ctgaccacc tgactgtcca 720
aacctgtgac cccaggccag ggaacgggga ggaaaccaa gaaaccatt ttcaggggagc 780

```



97

```

tcagacgtca caggagggag cgggagcagg atgtggccct ggcctcgcca gagcacctga 840
agaagcaggc cgtgagcgag gctgcgagtg ccctgggagc cgtttctcac gcatgaatgc 900
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ccatcgctgc tacactttgt ttttatttgt atttcatact gaagtttcaa maaaaaaaaa 1560
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1620
aaaaaaaaan n                                     1631

```

&lt;210&gt; 168

&lt;211&gt; 740

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 168

```

tttttgaatc ggttgtggcg gccgcggcga ggaatggcgg tatttgtgag aggagtcggc 60
gtttgaagag gtggaactcc tagggctttt ttgagagtgc tgatttagaa gaatacaaat 120
catggctgaa aatagtgtat taacatccac tactgggagg actagcttgg cagactcttc 180
catttttgat tctaaagtta ctgagatttc caaggaaaac ttacttattg gatctacttc 240
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gactttcagg attctgtctt taatgacctc tacaaggctg attgtagagt tattggacca 480
ccagttgtat taaattgttc acaaaaagga gagcctttgc cattttcatg tcgcccgttg 540
tattgtacaa gtatgatgaa tctagtacta tgctttactg gatttaggaa aaaagaagaa 600
ctagtcaggt tggtgacatt ggtccatcac awgggtggag ttattcgaaa agactttaat 660
tcaaaagkta cmcatttggg ggcaattgta cacaaggaga aaattcaggg ttgctgtgag 720
tctagggtact ccattatgag                                     740

```

&lt;210&gt; 169

&lt;211&gt; 2038

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1490)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1508)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1979)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1992)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2010)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 169

```

tcgacccacg acgtccggcg gcgggaagct ggcggcagcg gtcggtggcg gtggctgagc 60
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gatccaagag gagatgacgc aggatgggac gtggcgacac gtggcaccac aggctgcaga 360
gcgggcggcg ytcgaccgct tggctctccac ggagatcctg tgccgtgcag cgtggggggca 420
agagggggca catcctgtct ctggcttggg ggacggccac acacagggtc cagtcttctga 480
cctttgcca gtcacctcag cacaggcacc aaggcacctg cagagcagcg cctgggagat 540
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```

99

<210> 170  
 <211> 522  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (471)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (488)  
 <223> n equals a,t,g, or c

<400> 170  
 ggcacgaggt taatctaagg tgaagcaaac agaaaattgt ggaggttttg ttggtgtgca 60  
 actgaggaac atggctcaag aaactaatca cagccaagtg cctatgcttt gttccactgg 120  
 ctgtggattt tatggaaacc ctcgtaaaaa tggcatgtgt tcagtatgct ataaagaaca 180  
 tcttcaaaga cagaatagta gtaatggtag aataagccca cctgcaacct ctgtcagtag 240  
 tctgtctgaa tctttaccag ttcaatgcac agatggcagt gtgccagaag cccagtcagc 300  
 attagrcctc acatcttcat ctatgcagcc cagccctgtw tcaaatcagt cacttttatc 360  
 agaatctgta gcatcttctc aattggacag tacatctgtg gacaaagcag tacctgaaac 420  
 agaagatgtg caggcttcag tatcagacac agcacagcag ccatctgaag ngcaaagcaa 480  
 gtctcttnaa aaaccgaaac aaaaaaaga atcgtctgtt tt 522

<210> 171  
 <211> 1666  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (114)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1659)  
 <223> n equals a,t,g, or c

<400> 171  
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 gaccgcatct cccccacgg ggtcgggtgc tggggatcct gtccgcatcc actgcaacat 180  
 cacggagtca taccctgctg tgccccccat ctggtcggtg gagtctgatg accctaactt 240  
 ggctgctgtc ttggagaggc tgggtggacat aaagaaaggg aatactctgc tattgcagca 300  
 tctgaagagg atcatctccg acctgtgtaa actctataac ctccctcagc atccagatgt 360  
 ggagatgctg gatcaaccct tgccagcaga gcagtgcaca caggaagacg tgtcttcaga 420  
 agatgaagat gaggagatgc ctgaggacac agaagactta gatcactatg aaatgaaaga 480  
 ggaagagcca gctgagggca agaaatctga agatgatggc attggaaaag aaaacttggc 540

## 100

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catcctagag aaaattaaaa agaaccagag gcaagattac ttaaattggtg cagtgtcttg 600
ctcgggtgcag gccactgacc ggctgatgaa ggagctcagg gatataatcc gatcacagag 660
tttcaaaggc ggaaactatg cagtcgaact cgtgaatgac agtctgtatg attggaatgt 720
caaactcctc aaagttgacc aggacagcgc tttgcacaac gatctccaga tcctcaaaga 780
gaaagaagga gccgacttca ttctacttaa cttttccttt aaagataact ttccctttga 840
cccaccattt gtcaggggtg tgtctccagt cctctctgga gggatgttc tgggcggagg 900
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caacaaatct caatacagtc tgacaagagc acagcagtc tacaagtcct tgggtgcagat 1080
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ctagttctag agcggccgcc accgcggtgg agggccagnt tttgta 1666

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&lt;210&gt; 172

&lt;211&gt; 438

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (413)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (438)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 172

```

gcggaggagg tgtatgccca gctgcaaaaa atgcttcttg agcaacaaga gaagtgcctg 60
ctgttctcca agcagttcat gcaccagggc aacgtggctg agaccacccg atttgagaag 120
cttgctcagg accgcaagaa acagctggag atcctgcagc tggcccaggc tcagggcctc 180
maccctccca cccaccactt tgagttgaag acattccasa ctgtgaggat cttctcacia 240
ctcaacagca cagaaatgca tctgatcatt gtccggggaa tgaacctccc agccccctca 300
ggggtgactc ccgatgacct ggatgctttt gtgcggtttg agtttacta ccctgactcg 360
gaccaagctc aaaaaagcaa aacagctgtg gtgaacaaca caaactctcc cantttgatc 420
actcttcaac taaactcn 438

```

&lt;210&gt; 173

&lt;211&gt; 2511

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

101

<221> misc feature  
 <222> (12)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (28)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (44)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (2456)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (2488)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (2511)  
 <223> n equals a,t,g, or c

<400> 173  
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 gccagattcg gccgagcaag cggaacctct gggaaaagca atctgtggat aaggtcactt 120  
 cccccactaa ggtttgagac agttccagaa agaaccceaag ctcaagacgc aggacgagct 180  
 cagttgtaga gggctaattc gctctgtttt gtattttatgt tgattttacta aattggggttc 240  
 attatctttt atttttcaat atcccagtaa acccatgtat attatcacta tatttaataa 300  
 tcacagtcta gagatgttca tggtaaaagt actgcctttg cacaggagcc tgtttctaaa 360  
 gaaacccatg ctgtgaaata gagacttttc tactgatcat cataactctg tatctgagca 420  
 gtgataccaa ccacatctga agtcaacaga agatccaagt ttaaaattgc ctgcggaatg 480  
 tgtgcagtat ctagaaaaat gaaccgtagt ttttgttttt ttaaatacag aagtcattgt 540  
 gtttctgcac ttataataa agcatggaag aaattatctt agtaggcaat tgtaacactt 600  
 ttgaaaagta acccatttca gatttgaaat actgcaataa tggttgtctt taaaaaaaaa 660  
 aaagaaatgt actgttaagg tattactttt tttcatgctg atgattcata tctaaattac 720  
 attattatgt tagctgacag tggtagctgat tttttagggtt ggttgttttg tggatttctt 780  
 tagtagtgat agtagcctga accacatttt agataactca attatgtatg tatgtgcata 840  
 cacatatata aacacactaa tggtagaatg ctttttttatg tgctagacta ttatatttag 900  
 tagtatgtca ttgtaactag ccaatatcac agctttttgaa aaattaaaaa atcacactat 960  
 attaatattt catatttgcc aacagaaaca tggcagatag gtatcaatat gttttcaatg 1020  
 cctgatgacc tataagaaga aagtattgaa aagaagagag attagaactg ttagaaggag 1080  
 ttgaaatttt ctaaaagaca tagtatttag ttataatta aatgcattct tgaagtccag 1140  
 tgtgaatttt attaatgcta tcatctcgac caagctcaaa gcctacttat tagaaacaat 1200  
 gaagttcaca ataggtcata aggtctcttc cttttctaaa attgaaagac aagaaattta 1260

## 102

```

gtgccaatat tgtacagaca gaaattccat gtatgagtct caacaaagac tacctttggc 1320
taaattgtcta gaagcagaga agtaaagtga gcaaaatcca gtgttgagga gtcattgacag 1380
tactttgatc tttatatact ctgaagcatt tcttcaaact tttctacttt tatttgatcat 1440
tgatacctgt agtaagttga caatgtgggtg aaatttcaaaa attatatgta acttctacta 1500
gttttacttt ctcccccaag tcttttttaa ctcatgattt ttacacacac aatccagaac 1560
ttattatata gcctctaagt ctttattctt cacagtagat aatgaaagag tcctccagt 1620
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tcagtggact taaccaaaat tgtgttagtc tcaattccta ccacactgag ggagcctccc 1740
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atgagaagtg acatctgctg taaaaagtct atcttctctc taagtctgta aagagcaatt 1860
gaatcttcta gcttttagca acctaagcca aaggaaggaa agccacgaag aatgcagaag 1920
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acaagtgtcc caggtagcat tgactcccgat cattggagtg aaatggatca aagtttgaat 2040
taaggcctat ggtaaggtaa cattgctttg ttgtactttt gaacaagagc tcctcctgat 2100
cactattaca tatttttcta gaaaatctaa agttcagaag agaattgtatc actgctgact 2160
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catccacaat aaatggaatt ctttcttgca aaaaaaaaaa aaaaaagggc ggccgntcta 2460
gaggatccag gcttacgtac gcgtgccngc gacgtccata gccccttcta n 2511

```

&lt;210&gt; 174

&lt;211&gt; 230

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (4)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (19)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (227)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 174

```

tcntccag tggacttnt actaaattgt tgtcttgttt ttatttttta aataaactga 60
caaatgacaa aatggtgagc ttatgatgtt tacataaaag ttctataagc tgtgtatata 120
gttttttatg taaaatatta aaagactatg atgatgacat ttaaaaaaaaaa aaaaaaaaaa 180
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaanggg 230

```

&lt;210&gt; 175

&lt;211&gt; 1191

&lt;212&gt; DNA

103

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (44)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 175

```

ggcagagcgg cacgagatgt gagccacccat gcctgggtgt ctcnttcatt ctttaggcag 60
ttcattgtca cttccttcca ttggtaaaca tgtaaattat agtcgcatga tttagaattt 120
tactgaccaa agtcataata atagttaaca gtacaaggaa ctattttkgt ataatggttt 180
atttaataca gtatacatta tctttcatat actttgttac aatgttaaaa aaacttcatt 240
tttcataata taggaaataa agttggaaac aactctggtg ggaatacttc agatagagca 300
agaaagcatt cacagcaagg cctataatca gtaagatgtg tgaaaagttg ggtagccaca 360
ggaggtgttc attaaggata tgattccatt tatatagcta tttctattgc ataaccagga 420
cagttttatt gttttgaggt caatgttctt ttaaaatttg attttctgta agaagaggct 480
ttttggccca gaaagcctta cttattttac awcttccagt ttgtccatcc catgagttag 540
agttcgtctt gactctgcaa gctagaatca aagaattatg aaagtaagat catttagatt 600
tgaccaaggg caccattaaa tgggtgtcagg ttttaggaag cagacgggtg tataaaaaga 660
aaatgaacaa agatttctact tattggggat caggcataac tggatgcctg gattgtcctg 720
ccaccagct gccaccaata aaatcattca tcactctgca agagggacca gatgcttcca 780
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ayttcttcag ttgagttatc tgaaagtgtt gggcagtgac accatgccaa aactgttaa 960
attcatgcc ttaaaaacag tggagtgttc tgcaaagccc gattctctgc agctttaaga 1020
ctggacagta ttgaaatatt cacaggaatc ttccaagccg tgaaagctta atattaaaca 1080
gcccttttaa ttgcaaagga gaaaaaatg gagacacttg tgaaacctg cattctgagt 1140
gctgccacaa ataaattaag gaattccaga atttcttcat ctacttctgc a 1191

```

&lt;210&gt; 176

&lt;211&gt; 1499

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1462)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1476)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1495)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 176

```

gccttctccc gcctccctcg gccttagcca tggcgagtag cggcggtgct ggggcggcgg 60

```

104

```

cggcgggcgc ggcggggaat ctgaatgcgg tgcggggagac catggamggc tgctgaaaat 120
atgacaagct gactttctgg agaaattctg atgagatatg tcaagctctg caagrsgggt 180
tgaagattgc attgtagttg agaattgtaca wtgaaattwc tgcattgcagc agttagagaaa 240
aattttmctt tttaaaagaa ttataaaacc atagctttat aaatcagtg aaagtggctt 300
acagagagaa ctatcagatg tgtttacatc acatcttatt cacttttttt aacagctcta 360
atgcttttggc attgctatgk tcataatttat gtattcctta tttatagctc tgatagcttt 420
aattttctaa gcagtctgtc tatcagatgt gcacatctgc tgtgccaggt tgaagtatag 480
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acaggatttc agccaccact tgtgaatttt tatttagatt cattatgtat atcagaactt 660
tgttttttga aataagagca tggaaaacat ttcttgtaat ctactcttga acaaagaata 720
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gagtaaaaaa atcaaacctt gagaaacttg gattttaaaa gtaatgacaa tgcttagggt 840
agtatttttt gtaatttgaa tcattttacat ctaatgagaa tgttagtga gaattgtttc 900
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cttgaattgg tattttaataa attattagat gggtagtggt tttcaaaaga tacttgctat 1080
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caaaactaat atgggtttcc anctgatttt aagtanttcc ttgaaatttt tgggnttta 1499

```

&lt;210&gt; 177

&lt;211&gt; 1538

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (50)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (727)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1218)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1487)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 177



105

```
tgtaccggga cctgcagccc gtgggctcgg ggcctacgg cgcggtgtgn tcgtccgtgg 60
acggcgccacc gscgctaagg tggccatcaa gaakctgtat cgkcccttcc agtccgagct 120
gttcgccaag cgcgcctacc gcgagctgcg cctgctcaag cacatgcgcc acgagaacgt 180
gatcggkctg ctggacgtat tcaactcctga tgagaccctg gatgacttca cggactttta 240
cctgggtgatg ccgttcatgg gcaccgacct gggcaagctc atgaaacatg rgaagctagg 300
cgaggaccgg atccagttcc tcgtgtacca gatgstgaag ggytgaggt atatccacgc 360
tgccggcatc atccacagag acctgaagcc cggyaacctg gctgtgaacg aagactgtga 420
gctgaagatc ctggacttcg gcctggccag gcaggcagac agtgagatga ctgggtacgt 480
ggtgaccggg tggtagcggg ctcccagagg catcttgaat tggatgcgct acacgcagac 540
ggtggacatc tgggtccgtgg gctgcatcat ggcggagatg atcacaggca agacgtgtt 600
caagggcagc gaccacctgg accagctgaa ggagatcatg aaggtgacgg ggacgcctcc 660
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cgaattngka gaagaaggat tttgcctcta tcctgaccaa tgcaagccct ctggctgtga 780
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ggaaatagac cctttttag tagctccctgaaa aaaaaaaa 1538
```

&lt;210&gt; 178

&lt;211&gt; 896

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (194)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (825)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (828)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (831)

&lt;223&gt; n equals a,t,g, or c

## 106

&lt;400&gt; 178

```

ggacgcgtgg gctgcacctc accttgtcca cgtaccagcg caatacctgg ggtgacttct 60
tagaggccat actgcctctg gcagtgcagg ctgcaatgga agaaaatgtg gagtttcgga 120
gggggtctgcc ccgagacttc atggattaca tgggggcccc gcattcagat tctaaggatc 180
cgggaaaaaaa ccgntttcat ggagaagggtg cgggtcttgg ttgcccgctt gggacacttt 240
gctcctgttg atgctgtggc cgaccagcga gccaaagact tcattcacga ttctctgccc 300
cctgttttga ctgataggga gagggcacta agtgtttacg ggcttycaat tcgctgggag 360
gctggagaaac ctgtaaactg gggggccag ttgacaacag aaacagaagt ccatatgctt 420
caggatggga tagctcggct ggtgggtgag gggggccatt tgtttctcta ttacacagtg 480
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gctgatgccca tggaaactgtt gcttggttct tatccagagt ttgtgagagt gggggacctg 600
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ctgctcacta agatgcctct agccctaaat tagtttcttg ttgattgctg gaaacaaggc 720
agtagtgatt ctccgctgcc actgctaact tttttttttt ttttttttct cttaaactca 780
agttcttacc ttgataagca tcagtgtgct cacatttacc tttancantg ntcagtgtca 840
caaacctcgg aagggtctcta ggaagaacca tctcatctag gtacaaaagg gaaagg 896

```

&lt;210&gt; 179

&lt;211&gt; 568

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (67)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (469)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 179

```

ttatcttaga tttctagtta tttatatatt aactttttgt ttattcagaa tcatttttct 60
gtttgtngga atattttctaa gagccttggg aaaatctcga gtaaaatttt aaatgaaatt 120
tgtatagtgt tctgcctctt tccaaaggta tttctcaaaa ttgggaattg ttttattatt 180
gaagttgaat gacttcaggg gaactctaaa atgcaagatg ggaagcttct gtttggtttt 240
ttcctttccc tttggttaagg tcttttgctt cccatccccct tgaccacact ttgtgctgtc 300
tgttgtccag tctgctctcc kgatccctaa rgakgtttct tatctaggct gccatttatg 360
tgggtaaaag acaaggtaga aaatactctt ctgtatcttg tatcaagggt taatctaatt 420
tcttcatcac tttgttttga ratatttttg aatgttatcm acaattatna tagatggagc 480
atgtatgtct taggtttggt gttaatgttt aacatgcatt atcttattca atcctcacag 540
cagtcataaa atgtaggtgt ttttagagg 568

```

&lt;210&gt; 180

&lt;211&gt; 428

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

107

<221> misc feature  
 <222> (405)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (413)  
 <223> n equals a,t,g, or c

<400> 180  
 aaacacctat ggaaataatt ttgttttttt ttttttaaaa aggaatgaga tcatgtcctt 60  
 tgcaggggaca tggatgaagc tggaaccatt atcctcagca aactaacaga ggagcaggaa 120  
 accaaacacc acatgttctc acttgtaagc ggaactgaac aatgagaaca cacggacaca 180  
 gggatgagat caacacacac tggggcctga tgcagggggc gtagcgggga gagcatcagg 240  
 ataactagct aatgcatgtg gggcttaata cctaggtgat aggttgatag gtgcagcaaa 300  
 ccaccatggg acacgtttac ctatgtaaca aaccgcacat cctgcacttg tatccagaac 360  
 ttwaaatatt ttaaaaayct ttagagawtm caaaaaaaaaa ggttnttcaa tgnntcccca 420  
 ttaaattg 428

<210> 181  
 <211> 2901  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (10)  
 <223> n equals a,t,g, or c

<400> 181  
 agagaaagcn ttccattgaa aggtagatac tttgaggagt aaaaagactt ctttgaatgc 60  
 tggtaaacac cgcattttatt ttgtgtatgc agtttgattt gcacatgtat aaatggagat 120  
 gcttttcatt tttgtttgga ctgggtttgt gtcactgtct attacagttt gcttttttgt 180  
 gtgtttgctg tgcgtttgga gatattagtc agtttcttta gtgatatttg tttccttgat 240  
 gtgccttttc gtttttcttt ggggtttttg gaatctggat gctgttgaag ggcaatagca 300  
 gactcctcca gctaagagac aggacatgtt cttgagccac tgtagctgtt gaagctggac 360  
 accagacgct ccctataacc cccccgccag gccatagcgt gwatgcawgt gcacttccac 420  
 ccacagagga ggggtgtgaag ccttgagaac ctcaagaaag ggctggattc tgccatacct 480  
 ttgggtctac cttgggactg ctgggtgcca acgtgtcaac cagcctgtgt tccctgccac 540  
 ccacgcactt gctgaggtgt ggctgargca gaatcatgtg aatgggtgca tccaaggagt 600  
 tcagggccct gcttgagaga gaaatamttt agcatcatga aagggaaaga acgtgcaccc 660  
 cttttttgtt tcttttagtga atgcaagatt taataaaagt gaataatgag cttccccctt 720  
 gggagtggag ccagtgacag ctactgaca gggttgacat cagtatgatg tgttgactg 780  
 aaactgtatg tctgtaggta ggtgtgtgcc ttttagggca gaccacggtg gccaccccat 840  
 ttctccaagg tggtttacct agcttgtgtg tattagacat tgccaccctc acctctggcc 900  
 aaaaattctt gatttaaaaa gaaaagtcta ttttgttaac gacaggctct gttgtatgtg 960  
 ttactatccc aagcctggat tattttattt atttaaaagt attttaattt ccatattggc 1020  
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 tggacataaa tagattcatg ctcathtagg aagctgggag tttcgtgaag ctgaggggtg 1140  
 gttcctgtga ttcttgttcg cttcaacaaa aagtgggaga ccaagttttt atagcaaaaag 1200  
 accaaattag ctgtagagtc ttgaatgcag aaaaaaatta ccctagcttt cttagcactt 1260

108

```

agggttttgt gaggattcag tgttttagcac agtgcttggc catagtaagc cctagtaa at 1320
gttaa atatt gttattagt tttcgtaaaa cttgagaa at agagctgagc tcattccctt 1380
cctgttgatt caaaaataat acctacatga aaacatgatt ccaagttgat tgaatgttgt 1440
aggaattact ggtttagagt agcccagttc tcggcctacc ctgctgggtg ggatcttact 1500
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tcacttcggg ggttaagtaa tgcaggattc tgcaacaag gtgtcgccgt ccaa atgtac 2760
tgtcctggca tagagagcac tgctttgttt tccactgttg tagagaaaac tagggagaac 2820
tttatttttc aataaaacttt tcttgtgtga aaaaaaaaaa aaaaaaactc gagggggtgc 2880
ccgtacccaa ttcgccctat c 2901

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&lt;210&gt; 182

&lt;211&gt; 290

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (276)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (286)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 182

```

taatttaggt gacactatag aaggtacgcc tgcaggtagc ggtccggaat tcccgggtcg 60
accacgcgt ccgataaaac atgattttgt tttctaccct tcaaggtaaa cattaaaaat 120
aargtggtac ttgtgtwctt gtwcataaaa ccaaaattat akttgggaaa aaaataaatt 180
tatatatgaa aatgtcaaaa tcatttttaa agtattattt tcaataaaaa tggagaagct 240
ggtgaaaarw maaaaaaaaa aaaaaaaaaa aaggngngccc cttttngggg 290

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109

<210> 183  
 <211> 641  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (14)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (43)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (55)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (68)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (80)  
 <223> n equals a,t,g, or c

<400> 183  
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 tcccagcnaa tttgtgttcn ggtttgaaaa gacccaccac aaagctttty ctattttctg 120  
 atttaaaagt cgcttttgaa tatgaccatg agaaaccaag aaatgctgct tgtgtggtgc 180  
 tctgcttcct gaggatttgg ctggaagggg attctccgct ggcacatggg agaaggccat 240  
 cttctgtgtc ggtgctgtga tctgccctgt tctcacttgc tgaggataag ggcatacacg 300  
 ctgctcctcg ctttcttggt gcccgacttc gtactaagca gctcaggagc agtcactcag 360  
 acccaaatgt cttgactgtg ttgtttttta tcaactgtgac ccttaaagta caggccaagt 420  
 gttgtcaaac accttggtga aaacagtgga gggatgatgg taaagcagta gagggccctc 480  
 aacccacaca ctggctgaaa ctgccaccaa ctgccacgat gaacccaact gctgtttatg 540  
 cccccatttt cctttttttg tatctacacc cacacgattc ccaatgttgg atatttctac 600  
 atgaataaag caaggatcag tgcctcttat gtaaaaaaaaa a 641

<210> 184  
 <211> 522  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (514)

110

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 184

```

caccacgtgg ctgtgaaaat gacaaagcat ggtcgtgagc cactatgccc ggccggattt 60
gcccttatta atggttattt cttgtgaaag tttctttttg cctttgcatt cctttttattc 120
tgttttattcc cccatgcctc acccaaagag ttgcacggtc aattggcccg tgaaggggac 180
gcctacttttc aaacaaggca gacaggacac gacaggacgg cggctcatag cacagacttt 240
ggattgcagt ggatgggacc agatcctggc tccacttcts gcyagctgtg tggccctggg 300
caagctgctt aacctctctg ggccctcagtt tctccccctg taaactgggg gatgtgaaca 360
gcgcctgcct ccgagtccta aggattggga gtagtcgtgt aaagtgtca ggtccacagg 420
ccatcaatac taatagttaa aaattattct tagaatcttg ctccctcag ctccctgaaa 480
ggccactaag gcaccccagt tgcagaggcc aatnggtccg gg 522

```

&lt;210&gt; 185

&lt;211&gt; 735

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (197)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (293)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (386)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 185

```

agtataacca tttaggtgcc agatttgata atcaccagck gctcatksar gtcctatggt 60
gcaaagttac tcttacscct tttttacatt rcttgataaa ggcaatsttt aattayrtat 120
ttypctrttaa ctagctggta gagttcatac cttaaagtcag taaataatgt taagaatttt 180
ttccagctga gcaaatingta tgtatctagt tgtaagaaat caagaagagg atataaaaata 240
taatcaggat gtggactcta aaacggaata acctctatgt cctgtaactt ttntcactyg 300
taataatata gcattctcac cctrttaaat ggaaatttar agcacctyta aattccggaa 360
taaaattgct atttggatwg aaaaanccct taggcaacat ttattgaata ttaggaaata 420
actttttatgg gattagaatc cattttttat agaaaccaa tttaaaagta tacatatattt 480
aatataagtg ttgtgataat acagtaacca aaattgaaca cacagtttta wagcttttta 540
tatttagtag cagttgaata tatatggcat gttttacata gattaatttt actatttttc 600
tttrttttaa maagagracc aaattgaaag ccracagata ctgcaratga ctgggatttt 660
tgtttctgyc ttatcttttt gtgttttttt tctgaataaa atattcagag gaaatgcttt 720
tacagaaaaa aaaaaa 735

```

&lt;210&gt; 186

&lt;211&gt; 785

&lt;212&gt; DNA

111

&lt;213&gt; Homo sapiens

&lt;400&gt; 186

```

aattcggcac gagagcaagc ggaaccaggt atcgtacgtg cggccagccg agccggcggtt 60
tctggccccgc ttcaaggaac ggggtcggcta cagggagggg cccaccgtag agactaagag 120
aattcagcct cagccccag atgaagatgg ggatcacagt gacaaagaag atgaacagcc 180
tcaagtgggtg gttttaaaaa agggagacct gtcagttgaa gaagtcatga aaattaaagc 240
agaaataaag gctgccaag cagatgaaga accaactcca gccgatggaa gaatcatata 300
tcgaaaacca gtcaagcatc cctcagatga aaaatattca ggtttaacag caagctcaaa 360
aaagaagaag ccaaatgaag atgaagtaaa tcaggactcg gtcaaaaaga actcacaaaa 420
acaaattaaa aatagtagcc tcctttcttt tgacaacgaa gatgaaaatg agtaagtgt 480
aatatTTTTga atttagtcta ctttgaaaagt atatggagtg ttcattaaaa tcacattttt 540
tcctattata aagatactac aagttcttta tagaaagttt aggaaataga gaaaaaaatt 600
taataaacta catctattca tcaatacccc tctgacttaa aatgccaaact ctatagaaat 660
tagctagtat taacattttg ttatttccct tgtgtggttg tatatatatg taaattatat 720
ttttaagcaa aatacatttt ttgtgtgtaa acaaaatttt ataaatacaa ctgtatttga 780
aaaaa 785

```

&lt;210&gt; 187

&lt;211&gt; 1679

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 187

```

gatcttttagg tttttcctat agaaaacatt cttcctccat cagtagccct ttatttgata 60
ttcagaagtg gaaagctttt tcattctcca gtagaacttt taaaaattgt tacagatacc 120
tagctcttca cagatatcat gtattgtaaa cagtcagtgt tcttaatttt attttctcta 180
tttgagtgca taattatcct aataatccca aagacactga caactcaagg aacagcagta 240
cagtactatt agaagttaa g tatgttggtt ttatttcaca tttcatttaa ttgtggataa 300
atgttagaca tctgttgaaa taagctcata tgggtgaaaac gacaactata ttatgaatta 360
ttttcagaaa tggatctttg aatagcagat caggatttaa ataataaaat tatctatgaa 420
tcacttttat ggctacacat atatgatata aatccagagt tattgggtgca gaaatggcta 480
cccgagagct tggtaaatTT gccttggttt cttatgttaa atgtattgtg cttcccttct 540
gtctctagaa tgtggctctt cagaagacag acaatcgaca tttaaatttt tccaaacaat 600
gaaaaactaa attaaaaaca ttgcttgata tttcatttaa aattgcacct tgcttaaggt 660
ttactgaata actgaaatgt cagcaattta aaataaattc aattgtgtga taaaatatct 720
cacctataat agaagaaaag gaaaatcata ttatttggca attttgcagc attgtggttg 780
cctaacaggt atatccagca gatgagaaac agtatgaaag gattgtatta acatggtaag 840
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aatacgtttt cttgktttat catctgktct atgattcggc ttcactttgt gtggktattg 960
aattatgtaa cagagatttg gktttcccaa aatgktatca catttgaaac tatgattgct 1020
ttgkgktcag tccttttggg acacgtagct tycagcttaa gggtagagga aatatatacc 1080
taaaatcatc aatacatgaa agaaaaagga tggaaactat gtccctcagtt ttacttctac 1140
caaaacatcc ctgtatgtgt gtgcatgtat gttggcggtg gtgtgtgtgc atgcatatta 1200
gtaaatgtgt gtttgcattg gtgtgttggg gagtgtatgt gatctgggtg tttgtttatc 1260
tctgttatta tcccccttta gctttatttt agtcaactct acattatgat gaatttcaaa 1320
atgaagctgt attaaaataa ttgtaataa acaattcaat ctcacatgtt actgcagata 1380
gttaactttt gctgcaatct attgtacatt tgcaattttc tgtgttagta aacttagcag 1440
aatctggtta wttattttwg ttaggctta atgttcaactg aaagataagt caattactgy 1500
tagtaaaaaa ttaaggtact ctactgcag agatttaagc ctgggcctaa tgtgctgtat 1560
tatgaagcct tgtgactgaa aaatatgttt acatatgttg tctatttttt taataaactt 1620

```

112

ttatagctgg tctatttgct cagtaaaaaa aaaaaaaaaa aaaaaaaaaa aaactcgag 1679

<210> 188

<211> 780

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (289)

<223> n equals a,t,g, or c

<400> 188

```
cggtgggctc gcgttgaggc tgcggtcagt gagggagcag gagctggatc cggcttccgg 60
aaggagctgg tgagcaggct gctgcacctg cacttcaagg atgacaagac caaagtgagc 120
ggggacgcgc tgcagctcat ggtggagttg ctgaaggctt tcgttggtgga agcagcagtc 180
cgcggcgtgc ggcaggccca ggcagaagac gcgctccgtg tggacgtgga ccagctggag 240
aaggtgcttc gcagctgctc tggacttcta gggatctcag ccgtggckna ggccaccccc 300
agaggagccc ctggtccaca gaagcaggcc ttgtgtttcc agcggcctct gataagaggc 360
aggggaaggam ctgaaggatt tggarttgat tcaaacaaga tctctgggag tctccagcct 420
gtgcagaagg ggcaggactg cagtgcactg cgggccttgg agtgtccagt ggggacactg 480
gtgtgggaag gggcagcacc tggggagtcc ctgcctctcc tccctgggac aatagtgtgc 540
atgccacccg gggctcctaca ggcagggtgct gggaaaggcc tggccagcag gtagcctgtg 600
tgtttgacaa acagcagctg gcagcgtgc ctcctgccca cattcctgcc acccgacatc 660
aaagctggcg tgtgaccttt ccagccatgc gatattcccc ttggaagatg cttccccagg 720
ctataaattt gttctcacia agcaacatca ataaatcaaa actgtctcty ccaaaaaaaaa 780
```

<210> 189

<211> 533

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (485)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (498)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (522)

<223> n equals a,t,g, or c

<400> 189

```
gggtcccttta aggtttgctt ctacagcccc tggacttttag cctaaacacg gacccgcgaa 60
gctggcttta tttgtccatg tctcggacag agcctgggaa gctgccagtg agatttcaga 120
gaccaagagc gcgaaggggc gggcgatgtg gcaatccgtc tgggatgtga aaagcgtgga 180
```



113

```

ggcgcatttag aggcattcga cgaaaacaca ggaaatcact cctctcccgc tectggggcg 240
cgctgccact ggggcagagg actgggaacc gcggcagcgg gataagtggc ccagccagag 300
agcgcagctc ccgcgccccg tcctgccctg cgaaccacgc ggccccctgg gctgaagctg 360
ctccggccat ggccctcggc ccgcgccccg ccargggty gctgtcccct gcttgctggg 420
ctcctcccctg gtacattgcc tcctcccgga cacaattac tccctgaaaa aaaggccctt 480
tgttnaacct actgtggnta accgcctttc aaaaactaaa anttgctggg gaa 533

```

&lt;210&gt; 190

&lt;211&gt; 602

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (548)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (583)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (590)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (600)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 190

```

tccttaatct tggttttcct taaactttct ataagtccag catctgaaat attttgtcaa 60
ttatcacatt aatgtgttca ttttgtaagt aagagtactc aatttaaaat gatcttactt 120
taaaagtggc ctagtttgca gtgcccagca ggacactgac agtcacagct gtgtgacttt 180
ttgtgggtta cttaattttt ttgagcctec ttttctcttc tattcaatga ggataatagg 240
gcctacctca taggattatw atgcattccc ctctgttaat gcacgtaaag tttttacttg 300
gaaaactaac tcaccattta acaaccattc taagcaccat agaatatatt ttgtttcaca 360
aat ttggtat tcattcagaa taagtatttg aaaagtgagt aaattctatg caattatagt 420
tattaaatga cttataaaact gtgtttctct tccacttctt gctacattta atcttctagg 480
tgttcagata tctttggaga ttataggcag caataaagct aaggcagcta acctttaaca 540
ttcttgngt caagctaata ttttggtgaa agggaattct tgnggttctn aaaaaacttn 600
ga 602

```

&lt;210&gt; 191

&lt;211&gt; 858

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

114

<221> misc feature  
 <222> (772)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (801)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (814)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (815)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (852)  
 <223> n equals a,t,g, or c

<400> 191  
 cttggctcaa acaatatttt ccctataaca aaggcaatag gacacaaaat tcacatcctg 60  
 ctgggccttt tttcatcaag tcagggtgat ataaaaacat tggaagtctt ttcaccaaac 120  
 cctgacttta ttgaatgcta gtagaagatg tagaattaga gacatctgat ttgtttatca 180  
 ccttagcaga aaaaccacag tccaaaagac aagcaaatta agaattggagc ttaaccatgc 240  
 ctccattggg aagtctagac tttgagccag gtacagtaag aaaaattagc ctctgattca 300  
 ttaagtttgc cacatgactt attttgatat tttggataca ttaactcact taggagaatt 360  
 cagaaaagaa tgggtgatta aagttcatta cagctgaata aatgtgtcta aaacagactc 420  
 ttgtattctg aaagtacagt ctacaactga taaaacctta tgattctttt ctccccatt 480  
 atgccccat atatatcaag atttgggtac tttatttttag tagaaaatat atatctttta 540  
 catatgtatg tatttataaa tgcatagata tatgtataaa aatttgtaag cgttagcggc 600  
 attaattcac caatgcattt ggacaacttg atgtaactga ctttatttta tgtgactata 660  
 ataaaaagca taattttctc aaaaaaaaaa aaaaaaaaaa aaaaaagggc ggccgctcta 720  
 gaggatccaa gcttacgtac gcgtgcatgc gacgtcatag ctcttctata gngtcaccta 780  
 aattcaattc actggcccggt ngttttacaa cgtnttgact gggaaaaccc tggcggttacc 840  
 caacttaatc gncttgca 858

<210> 192  
 <211> 667  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (82)  
 <223> n equals a,t,g, or c

115

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (234)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 192

```
gcgggggaag cggggctgta gctgggcagg gagagggcgg acgaaatcgg tagcgatctc 60
ggctgcggcg ctgcccactt gncccgcccc gcggggcgcg ccctgaccct tcatctttgg 120
gcaggctcga gggcgcgcg acggttggcg ttctggggcc tcaaactcct gggccttgac 180
cgggcaggcc gcgtctcccc ggggtgtgagt ccaccgggac cgggccgccg cctnaagcgc 240
gkcgccaca gaagcggcgg cggccgaaga cgcgctcctg gctcggcccc acagcctcgc 300
ttggccgcca gttcttctgc agccgaaggc gggtgttctt ttaaagaatt attgaagacg 360
aaggtttttt tctttttatt tttttaatgg ytttacagaa tcttaaataa aatacagttt 420
gacatgacgg caaaaaatgt tggtttgact tccacaaatg cagaagtaag aggatttata 480
gatcagaatc tcagtcacaac aaaaggcaac atttcatttg ttgcatttcc agtttccaat 540
accaactcac ctacaaagat tttaacaaaa accttaggac caataaatgt gaatgttggg 600
cccaaatgt gatagaaaac gggctagaaa atttatagac tctgattttt cagaaagtaa 660
acgaagc 667
```

&lt;210&gt; 193

&lt;211&gt; 537

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (85)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (511)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (537)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 193

```
gttaccgctc tataccggca gcagccgcgg agagcatgcc ccgcccccggt ggagcccacc 60
ccgggcggtt aacctcggtt ctcantcccg ggctgtgacc ctccccgagg ccccgcccc 120
acggcggaagg cccggggcag ttaacccttc tcttgctgcg gcagagtccg caccggggca 180
ggcccatctc agaattaacg ctttgatggc atcaccgcgt cgggaatccc tggggatggg 240
gttctccacc gtcaagacct ttgagccgcc tgagcgacta actcctgcgc ccctgagggg 300
acattttatt cagaaattaa atcattcaga gttccagcac tgcgggggt catcgggctc 360
tgtccaccgc catagcctag cattgtcacc aacggagcca trgagggacc tcggcccaag 420
ctggggcctc ttcattgtcg aaaaggcctc ttgccagacc aggatctgtg ggcgcggcca 480
ggctggagga ctagggcggt ggcagtggca ngtgagtga catggctgtg ggtggtn 537
```

&lt;210&gt; 194

## 116

&lt;211&gt; 400

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 194

```

tctaactata ttaaaaaatt tctgtatggg gatatcatta ggaaggggat cagtaccttg 60
tctgtwatgt gtctactaag caaaacccaa actgcagcac cccctgtgg tacactgcac 120
ctccagtttg tactgggggt tggtggccag gctataggca tctttcacag gtccttgctt 180
agcatcccaa gtactgtgaa tacatgttga ttctttaaaa agacctggat tccaactcaa 240
ataaatcaca tcataatact ggcagagatc atcccaggaa atccaaaata ttccgttgct 300
tattttctga gctgttcggg gatcaaagtt taaatacttt tgcaactctg gagtccagtt 360
ttttacatca ttttactgt atcttccttt ccaacgtaac 400

```

&lt;210&gt; 195

&lt;211&gt; 431

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (411)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (417)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 195

```

cgcggtgggcg gacgcgtggg gtgaattttc agccctcaga gcagaaaatg agaaaataaa 60
actcgaacta catcagttta aacaacaagt aatggatgaa gtgatcaaag tccgaacaga 120
taccaaatta gacttcaacc tagaaaagag cagagtaaaa gaattgtatt cattgaacga 180
aaagaagctg ctggaattga gaacagaaat agtggcattg catgcccagc aagatcgggc 240
ccttaccag acagacagga agatcgaaac tgaggttgct ggcctcaaaa ccatgcttga 300
gtcacacaag cttgataata ttaaataatt agcaggggtc atwtttacst gcytaacagt 360
agctctggga ttttatcgcc tgtggatcta ataaagtgtc tatttaaagg ngaaaanaaa 420
aaaaaaaaag g 431

```

&lt;210&gt; 196

&lt;211&gt; 417

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 196

```

tttacttttc tacttttttc attttgttct gttcgaattt tttataagta tgtattactt 60
ttgtaatcag aattttttag aagtattttg ctgattttaa ggcttaggca tgttcaaacg 120
cctgcaaaac tacttatcac tcagcttttag tttttcta ccaagaaggc agggcagtta 180
accttttttg tgccaatgtg aaatgtaaat gattttatgt ttttctgct ttgtggatga 240
araatatttc tgagtggtag ttttttgaca ggtagaccat gtcttatctt gtttcaaaat 300
aagtatttct gattttgtaa aatgaaatat aaaatatgtc tcagatcttc caattaatta 360
gtaaggattc atccttaatc cttgctagtt taagcctgcc taagtcactt actaaaa 417

```

117

<210> 197  
 <211> 734  
 <212> DNA  
 <213> Homo sapiens

<400> 197  
 agacatattg aggtgcctgc ccttgtggag tattcatttt atgctgcca agatatcatt 60  
 taatttagac ttaacaagta tttccttgtg attatattac tctgtccttg ttaataaagt 120  
 gctgctgtgt ttgactctga acatactacc aaaacttctt caaagagttt tttatgaaag 180  
 acttttctcc tttaacaagar agaaatrugg tgctgccttt ctgttttagta aaagcagaat 240  
 ttgcagtggc atctaaagag acttttttaa ataaaaatta tgtattgtgg cataatcctt 300  
 tttttgagct ctacagagaa cagtcttttg gtaatagtgg caggatatta ttccttctga 360  
 atatataccc cattatagga ataactgtta cttatttagg attccatcat tgaaaatttt 420  
 gacccaaggc acagcagtga aatttatagt tcycaattta gttgtcatta ttgacaggca 480  
 ttggtattat tagtcattgc taagcaacta aaacttcac agttcaaata agttttaatt 540  
 gtcaaataaa gtataaacac atgaactttc tagaaatatt tcctcttttg gataggctct 600  
 taaccagttc atatataac tttgtcaaat atatggatgt gtatgtgtac atttataaga 660  
 accagtatgg atacatccat tcactgtggt acatttttaa ataaaatatt ttagcagtga 720  
 atatggaaaa aaaa 734

<210> 198  
 <211> 606  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (144)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (155)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (598)  
 <223> n equals a,t,g, or c

<400> 198  
 aggaagctgg gggaccattt tgcaccatga gtttgtgaaa aatctggatt aaaaaattac 60  
 tcttccagtg ttttctcatg cmaaatttyc tyctarcag tgataatgag taaactaaaa 120  
 ctatttgcag cttttcctca attnacattt tggtngtata cttcagagtg atgttatcta 180  
 agtttaagta gtttaagtat gttaaagtgt gatcttttac accacatcac agtgaacaca 240  
 ctggggagat gtgctttttt ggaaaactca aagggtgctag ctccctgatt caaagaaata 300  
 ttttctcatgt ttgttcattc tagtttatat tttcatttaa aatcctttag gtttaagtta 360  
 agcttttttaa aagttagtta aaagaattga gacacaatac taatactgta ggaattggtg 420  
 aggccctgac ttaaaaacttt ctttgtactg tgatttcctt ttgggtgtat tttgctaagt 480  
 gaaacttggt aaattttttg ttaactaaat ttttttctta aaataaagac tttttcacia 540

118

wraaaaaaaaaa aaaaaaaaaa actcgagggg gggcccgtac ccaatcgct gtgatgtntc 600  
gtatac 606

<210> 199  
<211> 373  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (251)  
<223> n equals a,t,g, or c

<400> 199  
catcttggag gtcaaataat agtaggaaaa gttcagcaga tactgaattt tctgatgagt 60  
gtactactgc agaaagagta ctgatgaaat ctccatctcc agcattacac ccacctcaga 120  
agtacaaaga tagaggaatt ttacatccta aacgaggtac tgaggaccga tcagatcagt 180  
cttctctgaa atctacagac agcagtagtt acccaagtcc ttgtgctagt cttctcctc 240  
catcctcagg naaagggctc aaaatctcct tcrccaagac caaacatgcc tgttcgatac 300  
ttcataatga agagtagcaa ttgagaaaac cttgaaattt ctcaacagaa gggatatctgg 360  
gctacaacty cta 373

<210> 200  
<211> 3652  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (306)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1412)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1519)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (2101)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (2102)  
<223> n equals a,t,g, or c

&lt;400&gt; 200

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acgagctgat gtctcccgga ggaatctgca attgcataat ttagttgggt gcttgtctac 60
tgtctctctc tttggcaaga atgaaagctc tatgagcaaa cagaccttgt ctgccttatg 120
atccattttta ttactagagc ctaggactgt taaattcatt aataaagtct ttccatcact 180
ttttgttctt tatattcctt tactcaattg atattcagca tgtgcagaac agttcttttc 240
caaggctgca taaaagtttt ggaatgaggc acataaataa tatccttcta ccaataaatg 300
ctatcngtta taaaatagtt tttattttat aatcactgaa tatgtcaaaa ctttacagtt 360
caggcctttt gaatcaaag caaaatcaaa tatgaaaagg ttaatgatct tgtccactaa 420
aattgtagtt tgccatacag gaaaatagac tcttaaaaaa gataaaaaaa aaaaaatcat 480
tcttaaggaa acatattaat aagacattta aaaaggctaa gatctttaat gtgaaaaata 540
ataagataaa gatgacaacc actgaagaga agaaaaaacg ttttatgttt tttctaaatg 600
tgtgtaaaaa caaaatcttg tactaccaaa aatgacactt ttttcaaaga aaggtatcaa 660
atgtgtatac tttaacacac agcccttctt tgtgtaaata tataggaaat ccttaaagga 720
gcataaaaca atttacttag aaattctata cttaaactta ttcaaaggaa ataattaaag 780
gtgtgtaaat aagatatgca tagcattgct ctaaatgtca aatagtaggg aactaggtaa 840
ataagatata tctatttagg gaattagtca agtaagatat acctatttag ctaattccat 900
gtagccatca aaaggatacc atagaacaga acttattgat gtgaaaagat gattaaaatg 960
tacttgttac taaaaacagc aggctgcaat actgtattaa ataatgagcc catgctgtat 1020
atctagacaa acatatatca taatgataat aataaatgta tgagacttat atttttgctt 1080
ctctgtattt tctaatttgt ctgtgataaa caaatattat taatgtaatg aagaataagc 1140
taaaatatac aaaaacaata acaactataa aaagaacccc ttcaatcaaa aagagatcat 1200
cagggattta attcaactat ggattggcac tattaggagg ccaaataatga ttcggtgaac 1260
tgaactgtag taaagacaag atattaggaa aatgtttaaa ttatgtgaga actattctca 1320
agcactttaa agatctattt gcaagataac aatgtgctaa ctttaagtaa tgtctatgta 1380
ttcttgagac cagctttgac aatgacagct gncattccat ttgacttggg cttacattat 1440
gttttgtcta ttttttcaaa aacagaaccc agggactgat tcttacaagc attttcttaa 1500
agattcactg ggtggctgna aatctgatca agctgttctt tgggagatca ttattcaaca 1560
cttatcacat actttatttc tacagctatg actgtcactc cccaagcttc acttcataat 1620
gaaaataaag aatacagccc ttttggaaaa gttggatggg aataccaagt gcgtaagttt 1680
ttagtacatg ccataatcaca accttctacg tggctgactt ttgacttttt catttctttt 1740
ataactgaca gaagacacaa aggcaaaaat gtcaacttca caaaaaatct tagtgctttt 1800
tggaagaagt gttatagatc atccagtcta accccctgat gttataaata tggaaattta 1860
ggcctagaaa ataggtaagt gatgaatcaa actagaagca ggtgtcctgc ctctaagccc 1920
aatccagttg ccacatcat ttactattta catggaacat caggttctac tttagaagtt 1980
aactatcaac ctacagggtt aaggaaaata gcaatgtgta tatacagacc ttgcatctgg 2040
tagctgtatg gtgcctgtcc aggttgaggg gtactgaagc ttgtgccata gctgagaaat 2100
nntgtctgtc caggtgactg agactgtgac aatccacctt cagtcttgat gcctgcccac 2160
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aaaaataaag ggtatacatg cattcagtga aataccataa agtacaactt cagtttttta 2340
aatccaggat tacagatttg aatgtctatt cacattatc tctcttgttt tattgcactt 2400
caagacatat cccttctata aaatgtaact ccagtgatat attttcatac ttaattttgt 2460
tgttttaatt atgtaagagt tgaagatcat ctcttcaca gtaaagaaat agccataatt 2520
aaatttttagc taaatgttcc caaagttgct atattgacta gtgttaaaaa taaaatcctt 2580
ttttatatta aaaatattaa ttagatccta taccatcaca gtatttttcc ctcttttact 2640
cttttacta caaagctgat ttcagtacca actcattttg aagtccaaag aagcaatact 2700
gggcacagaa ctaaacaaca tgggtgaaaag gcttttcttg aatatctagg tcctatcaga 2760
aaataagcac aaaggaagca gaacactaat gagctgaatc ttataaaaca gcagtgattt 2820
ataaacaagt gaggttgacc agcagtttcc ttttgtccct gttagtgtga aatatttgac 2880
tataattggt ttcgatgtag tctaaagtac ctttgttttt atcatatgat aatataaaaa 2940

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120

```
tgatgtatct gtggccccc aatacttccc caaacaccag gctaacatcg taattttggg 3000
acttggattht ggcagcactg aggtatgggg ctcagctctg tctttaatta attacaatta 3060
aagacagtca tacatgttaa caactctcct tcattctcac agagggaggg aagaaaaatt 3120
tctgccgagg gaattcacat tttttaataa ttttgcttcg tacttaagat aaatgatatc 3180
tttaggatct agaatacaca gtagtcttac tgtttatttc catttttagg gaatctcatc 3240
agcagagtac agctaggtaa ttgttttaag gcagtgggag aatctgactc ttggctgaga 3300
gtgcctactt taattcctgc agtatctcta aataacttca taatgacctt aacatttaag 3360
tcttaacaca accttaacat tttaaaaatg tgattttccc tgtaaagggtg atcccaaacc 3420
aatgaataac ccacacatag aaatgggtccc tggaaatata cctgccccag acagggtggca 3480
tgatggcttt agaaaatccc tttctttcca tgtgtgcacc cctagggatt ttccacctct 3540
tgctgcattt gagactatac tgatctgctt ccagccttca cctataccaa taaaatacca 3600
ataattcatg tatttttttt ttttgagacg gagtctcgct ctgtcaccca gg 3652
```

&lt;210&gt; 201

&lt;211&gt; 551

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 201

```
gctgcagcga cgtcgggagc agaagcagcg gcgacacgac gcgcagcagc tgcagcagct 60
caagcacctg gagtcccttt acgaaaaacc tcctcctggg cttatcaagg aagatgagac 120
taagccagaa gattgcatac cagatgtacc aggcaatgaa cacgccaggg aatttytggc 180
tcatgcacca actaaaggac tttggatgcc actggggaaa gaagtcaaag ttatgcagtg 240
ttggcgttgc aaacctatgg tcaccgaacg ggtgacaaa agatgcccttt ctttatcaaa 300
ggcaacaaaa agttagagca gttcagagtg gcacatgaag atcccatgta tgacatcata 360
cgagacaata aacgacatga aaaggacgta aggatacagc agttaaaca gttactggag 420
gattctacct cagatgaaga taggagcagc tccagttcct ctgaaggtaa agagaamcac 480
aagcaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 540
aaaagggggg g 551
```

&lt;210&gt; 202

&lt;211&gt; 665

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (463)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (471)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (582)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;



## 121

&lt;221&gt; misc feature

&lt;222&gt; (612)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 202

```

gcggcacgag aagtcacagg tcttgccaat actggtgtag tttcttgcct atatccgtaa 60
tttgaaggaa atggtragag tgattagaga agtgtaatta ctgtaatttt tccccctatt 120
gtagtttctt gcctgtatcc ataatttgaa ggaaatggta agagtgatta gtgaaatgta 180
attactgtaa ttttttcccc attcaacttt atatatcttt aactgatgac cagatcattg 240
ttgttctgaa ccagtttgtg gtcagcaagt gttttgtggg gttttgtttg tttgttttta 300
aagaacagtt tgggtcactt gacatggttc tccaaaggga tkttatgggt tgtwtttggt 360
tctgggtgat aaccgacttg ttagataatt tagataagca accgagttgc catgtttggt 420
tgtcaaactc caagtgtagc ttatatttta tgttcctaga gangttgtca nggaaagatt 480
tgaccttttg gcaaactctgt ttgaatagag atactaccat gctgccaat aaggctttct 540
ggccctgaaa aatatacgga attattcttg gaaatttgaa anggaaaaaa gaaataaact 600
gatccatggt tnttaccatg ccaaattaat tgaaggaatt ttcctaaaaa gtatctcccc 660
tcggt

```

&lt;210&gt; 203

&lt;211&gt; 2102

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1861)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 203

```

aaaaaaaaaa aaaaaagaaa aaaaccaaac taaccaaaac tctgtaaaaag agtgctttga 60
gctctacaaa taccaagtat ttattgtggt atatttttag aatgtagcca tacagtgtaa 120
ttatgggtat ctgtcatgga tcacaattat tattcatagt aagtcattgt gatacagaag 180
tttgtttctt cacttccccct taagaagcca actatagtaa tcatgcaaag ttgaggagta 240
tgtccttcag ggatataaaa agaaaaacaa atctgttttt tgagctaaaa gagcacatcc 300
aaacaagaat ttaactggct aaaatttagt aattactgtt aagtaactat caaacttgaa 360
atcttacaag ataaatgggt aagatgtctt gagtatttgg gatggggggc tgtgagctctg 420
attgagacat acatttttaca gagtagcagc actggaaaag gctagtccaa cctcccagcc 480
tctgcttggg tctccgctgc cccagccaca cacatcctag aattcttgta aacatatctg 540
gctctgtggt aacagtgcac ttgttatatg ttttctaaga gattagtctt tccgtgtgatt 600
tttccaagta cgctgaaagt agtagtatga acttaaggag gctagtcaaa gaaacttgga 660
gttataggta ttttttaaaga ataaatcctc aattccatca tcaactggcg gggagggggc 720
acttattaag catttttagat aataaaactg gttaagctta ctctggtaga acagacaatc 780
aaatctgggg attgctgaga acaataataa gctgaagtat ggctcacaga atcctaacac 840
aaatcattaa gtctctagtt agatttggtt tcctaaaatt tttcatagaa ttttaaaatc 900
taattctgac ttgtatggtt aagaaaagca gttaaatatt ttactactta tcaagggctt 960
ttaaaataaa taaatctgat tgataggaag aaaggcaaat aaatacctat gtagacattc 1020
tataataaca aagagccata gatgataaag gaattagatt ttaatgtaga atgggtggtt 1080
tctgaaacaa aggtatgtgg tactttgtag ttattgatga gaagccagta accagtagtg 1140
ttttcctaga tatatgccc cctcacaca actttcttca ttaacaaaca ttaaataatgc 1200
atttgatatc tattaaatta tattgtataa tgctgaagga aaacaaaaag tgttcaaata 1260
atcataactt ctacattaca ggttctgttt agatgcagaa ctagaggggc cagggtaaat 1320

```

## 122

```

gtagataaag agatatatag caccatgctt cttaatgctt catacttttg caaacagaaa 1380
aaaaaagttt tactttttatt ataaaacttc atctatgggc aaagtaaaca ctgttacatt 1440
taaattgctt tttaaaaaca attgcatctt aaaaagtcaa aaatctgaaa tttaataata 1500
tgagacttac actgaatata atgttcattt agaagttgct gtgggtccact tcatttataa 1560
ggaacaaata tttttacagt acactatagc aacagcaaaa gccctctctc accctgatag 1620
gaatgggttt gctgggtgct tagaagttag attcctgctg aatagaatta gccatcctta 1680
aaagatttta atccaatact gaactgttta taaaatgctt tctctattgt aatgtactgt 1740
aagtagtgaa attctgtata tactgctatt ttctgtctgt tcattgttgt gaacttctta 1800
tgtatattag tgaaataaat ttccagcttt catgttggtt cctaaacatt cataagtata 1860
nctaactatt aagagatttc ttcccttctt gagtaacaaa tttgggtgatt atattctttc 1920
tgatccaacc ccaaaaacta gctattctga aaaggctgat gttcactaat gggaagaatg 1980
aaatgaccct tcacctctta agggaaaaca gcctccgcca ttccctttca aaactatact 2040
tcttttactt gatactcaaa acttctgcac caaatcagt cagtattttt ccagaatgcc 2100
tt                                                    2102

```

<210> 204

<211> 283

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (181)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (282)

<223> n equals a,t,g, or c

<400> 204

```

aactgatatt taataatatt taatattgct ctaaaatttc tggctaaaat gaaaatattc 60
aaccatcagg aaggagaaac aaaactatta ctgtttgtaa acagtttatc atcagtactt 120
acctaaaaat cctggagaat gagctcagaa atatttctaa gagttgagac agtttagcaa 180
natgaacaga tacaacctca aaccaaacca aactagaaag ctgagaggac acagaatgcc 240
agtactgggc tgggcaacac ctctgttggt tgtgaaaatg tnc                    283

```

<210> 205

<211> 425

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (34)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (77)

<223> n equals a,t,g, or c

123

<220>  
<221> misc feature  
<222> (424)  
<223> n equals a,t,g, or c

<400> 205  
ccacaccccc ataaggccat ccaaataattt aaangccccc ccagtgggaa atttgggtgtt 60  
taaaacctca atggaancct aatatttccc ttatgtccgt tagtcccctg taaaatgtta 120  
ggtcacccca aggaaagggg agaaatagca atggttggtt ctaagggtatt gcttgccctc 180  
catgtcttcc taaagagcag aacttggagt ttctccttta tgtagagaag aagtwactta 240  
gggtgtatatt gcaatgaaat attcatagat attgaaagct tgtgtttaca tkaaatatgt 300  
ttattatcaa gaagtccttt ttccaattct gtacattaaa tatatgtgtt taaaaaaaaa 360  
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aagggggggg 420  
gggnc 425

<210> 206  
<211> 483  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (444)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (469)  
<223> n equals a,t,g, or c

<400> 206  
cccacgcgtg grcagaccgc gcagggagca cacaccgcca gtctgtgcgc tgagtcggag 60  
ccagaggccg cggggacacc gggccatgca cgcccccaac tgaagctgca tctcaaagcc 120  
gaagattcca gcagcccagg ggatttcaaa gagctcagac tcagaggaac atctgcggag 180  
agacccccga agccctctcc agggcagtc tcatccagac gctccgctag tgcagacagg 240  
agcgcgcagt ggccccggct cgccgcgcya tggagcggat cccagcgcg caaccacccc 300  
ccgcctgcct gcccaaagca ccgggactgg agcacggaga cctaccaggg atgtaccctg 360  
cccacatgta ccaagtgtac aagtcaagac ggggaataaa gcggasgrrg gacagcaagg 420  
agacctacaa attgccgsam cggntcatcg agaaaagaga cktgacggnt taamgaktga 480  
tcg 483

<210> 207  
<211> 976  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (193)  
<223> n equals a,t,g, or c

124

<220>  
 <221> misc feature  
 <222> (929)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (958)  
 <223> n equals a,t,g, or c

<400> 207  
 agcttttcagc aagagatggt cacaatcaga aggataatac aaagtcaaaa gagaaggaga 60  
 gtgaaaacgc ttccaggaga tggtaaagga aataagcata agaaacacag aaaaagaaga 120  
 aaaggggagg aaagtgaggg ttttctgaac ccagagttat tagagacttc taggaaatca 180  
 agagaaccta cangtggtga agaaaataaa acagactcat tgtttgttct cccaagtaga 240  
 gatgatgcc aacctgttag agatgaacca atggatgcag aatcawtcac ttttaaatcm 300  
 gtgtctgaaa aagacmagag agaaagggat aaacccaaaag caaagggtga taaaaccaa 360  
 cggaagaatg atggatctgc tgtgtccaaa aaagaaaata ttgtaaaacc tgctaaagga 420  
 ccccaagaaa aagtagatgg agaacgtgag agatctccct cgatctgaac ctcccaatta 480  
 aaaaagccca aagaggagac tccgaagact gacaatacta aatcatcatc ttcctctcag 540  
 aaggatgaaa aaatcactgg aacccccaga aaagctcact ctaaatcagc aaaagaacac 600  
 caagaaacaa aaccagtcaa agaggaaaaa gtgaagaagg actattccaa agatgtcaaa 660  
 tcagaaaagc taacaactaa ggaagaaaag gccaaagaag ctaatgagaa aaacaaacca 720  
 cttgataata agggagaaaa aagaaaaaga aaaactgaag aaaaaggcgt agataaagat 780  
 tttgagtctt cttcaatgaa aatctcgaaa ctagaagtga ctgaaatagt gaaaccatgc 840  
 accaaagcgc aaaatggaac ctgatactga aaaaatggwt aggaccctg aaaaggacaa 900  
 atttctttta gtgcgccacc aaaaaaatnc aaactcaaca grgaaactgg gaagaaantt 960  
 gggagttmcc gaaatt 976

<210> 208  
 <211> 660  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (560)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (567)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (583)  
 <223> n equals a,t,g, or c

<220>

125

&lt;221&gt; misc feature

&lt;222&gt; (589)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 208

```

ccacgcgtcc gccgacacgt cgggattggc ggctgcagcc aggggtcctc cgacgctggg 60
cttccgtgag cggcgctctg ccaggtgggg ccggagctgc ggggagggag ttggcgccta 120
gcgcgcactc catccccgcc tctgcagtgg actcggccgc agaatcgggg tcccgggctc 180
ctggaacttg tcccscaccag gccgcggcga ggaggtcact ccagccgac tctggaccgg 240
attcgtccca ttctcgtcct catggtggac aagaaactgg tgggtggttt cggaggcaca 300
ggtgcccagg gtggctccgt ggcccgcaca ctcttggaag atgggacatt caagggtcga 360
gtggtgaccc gaaaccctag gaagaaggca gcaaaggagc tgaggctgca aggtgcagaa 420
gtagtgcagg gagaccaaga tgaccaggtc atcatggagc tggccctgaa tggggcttac 480
gscaccttya tcgtgaccaa ttatgggaga gctkcagcca ggagcaggag gtmaagcagg 540
ggaagcttct tgctgatctn gccaaagngcc ttgggcttca ctntgtggnc ttcaaggggc 600
cttgaggaca ataaagaagg ttacgggaag ggagatttgc cgccggggaa cttttaccgg 660

```

&lt;210&gt; 209

&lt;211&gt; 514

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (56)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (464)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (467)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 209

```

tggaaccaat ctttgtggta catattccag ctttttgaat gagtgcata cagtnagta 60
cctttaaagt aacactttgt acataacaar tactcagcaa atgtgaaact ttatttgctc 120
ttacttcaaa attagtccaa aatggtggaa ataaaatata agacattgat ctagatatga 180
ggtttttctc cttcattctc agctgtcgaa gaaatcraag tagcatatgc acaaggwtaa 240
aaaccacata tacaaatact atagaacagc ttataatgaa aaccttgcct gcctttataa 300
aaaatgtgat tatcttcttc tgtaaatgtc aataaaagat ggtttgtcct agaaggctca 360
taaagtgtat tatgttcttg aggggtttaca tatgaaaaat gtagaaaata caaaaagtgt 420
ctatatatac aaaaatgtaa gtgttaacat ttttatattt gcctcnagc ttttttttta 480
aataaaagga atgccatatt gccattaaaa aaaa 514

```

&lt;210&gt; 210

&lt;211&gt; 173

&lt;212&gt; DNA

126

&lt;213&gt; Homo sapiens

&lt;400&gt; 210

```

gtcaatgctc tgaaatctgt ggagcaaacc acagtttcat gcccatcgtc ctagaattaa 60
ttccccataa aatctttgaa atagggcccg tatttaccct atagcacccc ctctaccccc 120
tctagagcca aaaaaaaaaa aaaaaaaaaa aaaaccctgg gggggggggc cgg 173

```

&lt;210&gt; 211

&lt;211&gt; 1521

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 211

```

gctatcaaaa tcatgacatt atgtcacttg gagcaacaca gttgaccgcg caaggcagcc 60
tcttcctcca tagatggatg aacgctgtgg ccgctgctcc tkcmctggcc atgccctgay 120
gctgccaaca ccactgctcc tctatttata agtcttarta gaggttgctga cccagcaata 180
actgaacagc tgatatgtac ctcacactaa gccaggcgct tcatatgtat ctaacttgaa 240
aaatgctgag ctagttacct taacaccatt aacttttact taaaagtttg tttttctttt 300
ttaatccag tgagctccaa acaagtttta ggaggctccc caaaaccagt gaagacttta 360
actaaaagta gaatttcaaa gtattagaaa ccaaacccca aaattaaatg tgaagatcag 420
tgtctgtact gagctggccc atctgggtgga cacaggattt gcgttatcga ctgcaatgtt 480
accaggatt cacgatttct agcatctgtc aggggttaaga aaattggatt gagtaccaa 540
tacagcagag caaaccgggc tttgaggcaa gggccccatc aagtagtcat gcagtacttt 600
tgtaggggtt ctgggtgcaa atcttctctg tccctccac cttctcctgg cctccttgta 660
aacccaaacc gccagggtacc tcaattttct tcaagaccag gctgttctta atgttggtta 720
attggtcaag gaaatgggtg agccactgct tgctctgcac atcgtcctca gagtgtcgg 780
tcttcaggca gtacagcagc tgcattggct tggcctgcag gagtaagtgg cccattccta 840
ggctgtcccc aaagatgtgt cctctgaaga agctggctcag gtagaggggg tgtccactat 900
ggttatagat ggtgaaggag atgctgcccc ggtcgagcgt tttgtccacc tgccagggtg 960
acaggagtgg gttgggggca ccacgcagag catcttgtac ctgcgcaca cctgctggta 1020
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actgacttca gcaaatgtgt ctgggttcag cagcgagttg ctgtgtgagg ccaccagaat 1140
ggaggtgata tcggcctcag tgctcatcct ggaggtggag aagtgggtcag agtcctctgt 1200
ggtgaaatgg ccctacacca aagtgggaga cattcagaat cgaggcgaaa ttggcctcag 1260
tgctcctctt ggaggcagag aagcagtagg agtcgggtgg gaaatggccc tgtgtgaatg 1320
tggaagacca gcagattgga ggtggaattg gcctcagtgc ttgtcctgga ggtggagaag 1380
cggtcagagt ccttgggtgg gaagtggccc tgcacaaaac gttgtctccc cttggccggg 1440
gaaagaataa aagaaagctg gccacttgca aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1500
aaaaaaaaaa aaaaaactcg a 1521

```

&lt;210&gt; 212

&lt;211&gt; 1875

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1052)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

127

<221> misc feature  
<222> (1291)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1849)  
<223> n equals a,t,g, or c

<400> 212  
gtctgctgtt gtcagaagggc agggaggggtg atgaaggact gaccacacatg gactgggatg 60  
tgtgtcgggt atgggcatga ctgcacgttc actctcagtg ggatctgggc aacatggagt 120  
tcattgtcct gttgcttact tactgcaatg tctttggccc tctttttcaa ctgggtcctc 180  
tgttggggccc aaagggttggg agtaggagac agtatcccag gctgacaagg gcttgccytt 240  
taccttgggc accttggttaa tttttagcct gtgccccttc ccacctttgc cctcccagtg 300  
gttggatatg gggaagccca tctcagttcc tgtgacttca tgtctcaaac caaggatgag 360  
cgtctggtct ctgctatgat ggtgggtatcc gaggcctttc cctgcccagt ctgggtgcctg 420  
ccccacattg taccggacac tggattcctg gacccccttc tcttttcctt tctttccttc 480  
aggtcacgca gccctgtact gtatccagca ccacagaaac ctcagtgttt ttcctctgct 540  
ggtttggggc acaaggaagc cttagggtat ggggaaaggc tgttattacc tagagtttac 600  
tcccaggcca gggggctgcc atcttcttca cagacatccc tgaaaggaag cccctttggg 660  
gcagggaggt gaggacttca tctcaacatc ggctggtggt tggtagggga gcttttyctt 720  
ttctttcctt tttttttgtt tttgtttttg tttttgtttt tggtaacatg ttaggagtta 780  
atgttgcaaa gagtagttta catcttcaact ttctgaagac acttgaattt aggaccgatg 840  
tatctgtgac aagcatgcca gaagtggcag gggccatcag ggctaaccac ttcacaccta 900  
ccatcgtccc atggggatcc aagacctgag ataaagcaac agcctgcccc gatccctctg 960  
ttcatcctat cctttccaag gttgggtccat gccaacataa cctctgggca tcagacatca 1020  
gcaggtctgt gtgcctcagc cctgttaagg gncaggtttc tctttagccc tcttcttgca 1080  
cttgggagca aaggcactac cagtagagaa gggccatcca gccgtgcccc agcctggacc 1140  
cctggggctc agatagaggt gctgagcccc tgtgtcaaag ttgttaaagtt tttttgtttt 1200  
gttccattgt agctcttttt tttttttttt tccctttcct ggtgattgat ttacaaaag 1260  
aaagtaagct gcttagaagg ccctggaagg naagtgagga ggagggacaa ggaagatgac 1320  
tagttacgga ggggtgaggt tgttttttgc caaaaagcct gggtagagtg atctgaatta 1380  
tctggcacc cctgaatgg aaccccagag tacctcctgt gtggaagggt ccctggattt 1440  
tccctaacac ccacctctc ccccttcagc catgctgatg gcagagaaga taagaacttg 1500  
gagcccatth ctcactggag agggaaaact gtcactctggc tttgcggaga aggttccacc 1560  
ttacgctcgt agtacattat ctttactatg tgctaggata tcatatttaa aaggacaaaa 1620  
aaatgtaaaa tacttgaatg agcttgattt ataacattaa tattattgag agtatctgct 1680  
ttccaggctg aagtgattca ttcattatc tagtcctgct ttagtccttt gtaatttgtg 1740  
gtaattatgc ttttcttttt aatacaaaaa aatgtataaa aataaacact tgaaaaggca 1800  
aaaaaaaaaa aaaaaaaaaa aaaactcgag gggggggcccg tacccaatnc gccggatagt 1860  
gatcgataaa caatc 1875

<210> 213  
<211> 1917  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (798)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (802)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1073)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1748)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1829)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1887)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1891)

<223> n equals a,t,g, or c

<400> 213

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atgcaattgt cctgcctcag cctcccaagt agctgggatt acagacatgt gccaccatgc 120
ccggctaatt tttgtatttt tagtagagac ggggtttcac tatgttggtc aggctgatct 180
caaactcctg acctcaagtg atccaccccc ctcggcctcc caaagtgcta ggattacagg 240
catgagccac catgtctggc cctacttttc ttttatgcct tctttttgga ttaatcaaat 300
atttagtttc attaccccac tattaacttt ttctattata tattcttttt ttaattaagt 360
gattaccctt gggttgttac atacatcctg aacttcttat agtaaataata catgattaat 420
ttaacctctt ccctagcaat gctcagattt tagaacatta taattccatt tagtctcttc 480
taccttttgt tttattgttt tcatgtattg taatcctaaa catattttac accccacaag 540
acaatatatt agtgttgcac atcctcaata ttcatttaga ttaatccata caattactct 600
ttctattgtc tttcactcct tactgaattt ctaggctttt atctgaaatt attttccttc 660
tgccctgaaga actacctttt atagtaattt tagtgtaatt ctgcttarga agtattatct 720
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gggtgtatttt ctgggtcngt antyctagat tacagttact ttcttacta cttatatctt 840
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aatgtgccaa gatgtgmctt tctttawatt catcctgctt gggattttca ggaattcatg 1020
cctcagggct ttatgtcttt cattagtttt gggaaaattt taagccatta acntttcaaa 1080

```



129

```

gatcatctct  tccctattct  ctcttctct  ctctgctatc  cttttgraac  tccaattmca  1140
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atctttttcc  ctctctgagt  gtcagctctg  tgataaggta  gtcttgagga  cttgtgtctg  1260
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tacttattca  tctcttactg  accttggagc  tcagtgtaa  caggcaatga  aacctaaaggc  1620
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ccagttgcag  aagattttact  tattcaagtc  atttaagaaa  accttctaac  ccaaaatttc  1740
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acataattct  gtggagatct  gaggctttta  ctagcttgaa  tgtacaacac  acaacctgtg  1860
ggtgggataa  attaagcata  aac.ttgngta  naaaaaaaaa  actcaggggc  cggccat      1917

```

&lt;210&gt; 214

&lt;211&gt; 1544

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 214

```

ggcacgagct  atagcaatct  ggggttttctt  agccaattga  aatgggcatt  tattagatca  60
tttaagcatc  atatcaatat  agtatattttg  gcgactttat  gataagttct  tatgatagat  120
gttcaaaact  ctgctcaggt  gacatttttta  tggatccaca  tagtttttgt  catatatgaa  180
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catgagaatg  gaccgacttg  tagttgtatt  aactttttcta  gtgccaggt  tagaaagttt  300
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agatttagaa  gctgtctata  ttttccccat  tatccataat  acatattatt  ggcaatatgg  420
ttttcactct  ttgttggttaa  cgtatcaaca  atgtgcaata  gccactaata  atcatttgtt  480
aatgcatgct  tccaagttct  gtatttgaaa  atctcagact  tcatatatgg  taagtgatgg  540
agtaatttat  aactttttatg  ttgaattctt  gctactttta  aaaattgtgc  ttctcctttt  600
ttaaagcata  tgacttactt  aacagctgat  agtcagttac  ctggattttt  agtatttttt  660
tacatcacaa  aaagattttct  ctgaagtttg  cgcaggggtc  tatttgtagg  cagtttccaa  720
cttactaata  agtaaggttc  tgaaagttat  aagttagctg  tctggaatag  atagtctcat  780
agaaaccagg  ttgtagatgg  tgatttggtt  ccttgggcaa  cctactgaaa  cccatttact  840
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gcctgtaatc  ccagctactc  aggaggcgga  ggcaggagaa  tggcgcgaa  ccgggaggcg  1440
gagcttgcat  tgagccgaga  tggctccact  gcactccagc  ctgggcgaca  cagcgagact  1500
ccgtctcaaa  aaaaaaaaaa  aaaaaaaaaa  aaaaaaaaaa  aaaa      1544

```

&lt;210&gt; 215

&lt;211&gt; 1762

&lt;212&gt; DNA

130

&lt;213&gt; Homo sapiens

&lt;400&gt; 215

```
catgagccac tgcacccagc cgataactact atatccccat tttacagatg agcacatggg 60
caaattgagg gtaaggcact gacccatgat catcacagctg agaagtggca aaggcaggat 120
ttgaacctag aacctctggc tccacacact agtaatctaa accactctcc ctacaataca 180
acatacgtgg taaagatgtg tgggtgggcac gcaatcaacg taggtccctt cacagttgct 240
gggagaggca ggaatttgca gttcctccgc gttctcctcc tccgctgcc acctgtcctg 300
ggtcattcct gcagcctgcc ctgccctgcc tgggtctcacc ctccctctgc caacagaagt 360
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cctctttgca ggaggcgta ggggagggga cccaggtgat ttgggtcctg gctggtcacc 480
agggaagctg gcaagggaag ggagactagg gtgcgctcta ggagaagccg acagcctgag 540
agtcccagaa gaggagccct gtggaccctc ccctgccagc cactccctta ccctgggtat 600
aagagccacc accgcctgcc atccgccacc atctccact cctgcagctc ttctcacagg 660
accagccact agcgcagcct cgagcgatgg cctatgtccc cgcaccgggc taccagccca 720
cctacaaccc gacgtgcct tactaccagc ccatccccgg cgggctcaac gtgggaatgt 780
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tccaggggtg tgtcaccttg tcctatgtcc agatctaate tattcctggg gccataactc 1680
atgggaaaac agaattatcc cctaggactc ctttctaagc ccctaataaa atgtctgagg 1740
gtgtctcatg aaaaaaaaaa aa 1762
```

&lt;210&gt; 216

&lt;211&gt; 253

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (236)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (238)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 216

```
gggtaaatga gtgccagggc cggcaagccc ccgctccccg ggctctcggg gtcgcgcgag 60
```

## 131

```

gatgcttggc acgtaccccc tgtacatact tcccggggcgc ccagcatgga aataaagcac 120
ccascrctgc cctgggcccc tgcgaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 180
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaagggg ggccgntnta 240
aaaggttccc tcg                                     253

```

&lt;210&gt; 217

&lt;211&gt; 511

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (471)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 217

```

ccccagcggg cgcggggccgg agcacgggga cccagcatgg gggtagtgct cacacagagg 60
acgctgctca gtctggtsct tgcactcctg tttccaagca tggcgagcat ggcggtata 120
ggcagctgct cgaaagagta ccgcgtgctc cttggccagc tccagaagca gacagatctc 180
atgcaggaca ccagcagact cctggacccc tatgtaagca cctgggccct tgtggcatct 240
gagtctcaga gaactatggg gttaggaagg gagtgagaag cagggaggac aggcctagcc 300
ccactccata tggccagggtc ggggaaactga gtcgctatgt tattccagcc ttaaccctga 360
ggagctaagg ctggccctcc agctttccta gctctgtggt cccggggcgg gactccggac 420
accatcacca tgctmactgc ttactcagtg tgtttcctgc acacctgcca ngcttctggt 480
ctaggcaatg ggacgtagca gtgaagcaag a                                     511

```

&lt;210&gt; 218

&lt;211&gt; 2945

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 218

```

ggaattccaa ctatggcctg ctgcctgttt ttggctgggt agctaagaat gattttttaca 60
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tgaagttcaa atctcagtggt ctagaaataa agttttattc gcacacagcc tgctcatttg 180
tttacctatt gtgcatggcc actttcacat tacagtggca gaggttgaaca gctgctgcag 240
agactagcca caaaactaat aacgtttact gcttggccct tacagaactt tgccgagccc 300
tcattttaaag taatagattt aaacagtcct cataagcagc tgctggcttt gaaggtaggt 360
gcagccacta gtgcttttct tggcagattc attgccaagg aacagtttgt taagtaattc 420
ccttgtttttg tgtgccaggc tccataaaga aagggttctc acgctcaa atatgggcaa 480
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aaagattgac aatcacagtg ctgagaaggc ctccaataga gaagttgggt tagttgttcc 660
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gccagtaaagt gaggagcttt taaagccctt tctttgtggg agggggccaca agggggccagg 840
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ggtgtccccct cccaagagct tgaagatcct gtctccttcc tcctctgtcc caacctggct 1080
tggatatattg ttgaatgaat aataacacct gccacttata agtgtttatt ggggtgctgag 1140

```

## 132

```

ctgatctcat tggatttttt ttttttcttg agacagagtc ttgctctgtc acccagtcac 1200
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gttctcgtta tccccagggt acaggcaact gagggccaga agaagggttg taatatgtta 1560
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cactgcactc cagcctggat gacagagtga tactccatct caaaaaaaaa aaaaaaaaaa 2940
aaaaa 2945

```

&lt;210&gt; 219

&lt;211&gt; 445

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 219

```

ggtaccgggt ccggaattcc cgggtcgacc cacgcgtccg ggaactgtga cttccccacc 60
ccaaattcta tggccggcta atgttttgct atgggtgacta tcacctatct acctggaagc 120
accagaatgg cttagtacag ctagggagct cagccagatc tcggtgtctg ctgtttgaga 180
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ctgcagtggg tctgcatttt agtggggaat ttgttttggg tcattttggc attcccgcaa 360
ccatcttggt gggttttttg taaaatgtgg cacccttcc agacctytta gctgtggaam 420
tgagrtattt tagcaggggc cgggt 445

```

&lt;210&gt; 220

&lt;211&gt; 522

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

<220>  
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 <222> (402)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (417)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (480)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (482)  
 <223> n equals a,t,g, or c

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 aattaatgta tataattaga tattattagc tactcttagg tagcttcatt tggtgaaagt 120  
 ttgacaagtg aatgaagttc acatctggaa atcggtgaac atttttcggt catggaactc 180  
 aatggctacg ttagtcgttt atgcttttca ctggttggtt aggggctttg gaagtaaagt 240  
 ccatcaacaa tggatacaga agacctggat ttggaataag ggcaaaaattt atttgatggg 300  
 gctgaattgc tctgccagga gcatttggtg tgagatgaaa tggctctctt gagactgagc 360  
 tgccacctgg gcaatatagg ccgctaaggg tctctttatt cnccttactt ggacttnctt 420  
 tcctggaggg aatctcccga aaaaggaaac tttccttccc cagggggggc ccaatggttn 480  
 cnagggtggt cttcaaaatg ggttccccaa ctggtggcat ca 522

<210> 221  
 <211> 1516  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (1493)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1497)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1508)  
 <223> n equals a,t,g, or c

134

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1509)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1516)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 221

```

gaatgagcag gataactgtg tcctgattca tgatgtggac caaaggaaca gcgataaaga 60
tatctttggg gatgcctgtg ataactgcct gagtgtctta rataacgacc agaaagacac 120
cgatgggggat ggaagaggag atgcctgtga tgatgacatg gatggagatg gaataaaaaa 180
cattctggac aactgcccaa aatttcccaa tcgtgaccaa cgggacaagg atggtgatgg 240
tgtgggggat gcctgtgaca gttgtcctga tgtcagcaac cctaaccagt ctgatgtgga 300
taatgatctg gttggggact cctgtgacac caatcaggac agtgatggag atgggcacca 360
ggacagcaca gacaactgcc ccaccgtcat taacagtgcc cagctggaca ccgataagga 420
tggaattggg gacgagtgtg atgatgatga tgacaatgat ggtatcccag acctggtgcc 480
ccctggacca gacaactgcc ggctggtccc caaccagcc caggaggata gcaacagcga 540
cggagtggga gacatctgtg agtctgactt tgaccaggac caggtcatcg atcggatcga 600
cgtctgcccc gagaacgcag aggtcacccct gaccgacttc agggcttacc agaccgtggg 660
cctggatcct gaaggggatg cccagatcga tcccactgg gtggtcctga accagggcat 720
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tggagttgac ttcgaaggga ctttccatgt gaatacccag acagatgatg actatgcagg 840
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atgtgaatgt ggcaataaag gagaagagat cattttttaa aaaaaaaaaa aanttcnggg 1500
gggcccgnnc caattn                                     1516

```

&lt;210&gt; 222

&lt;211&gt; 1387

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 222

```

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tcagctgctg tcgtcccagg gtggagccca ctgctacttc aggaggggcc tgctcaggtg 180
tagttaccac aggtgatggc tgagttcaga aacaaccagc gggagagtga aggaagaaag 240
gcaaaaagca tgaagggaca gacaactggg aagaaccagg acaatcctgt gattgatgaa 300
atagacttcc ttgaagcttt taaaaatatt cagccctcat cgtttcgaag cgtcattgga 360

```

## 135

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ttaatggata tcaagcctgt tgactgggag gagattggtg gccttgaaga tgtaaaactg 420
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ctgacacaaac caaagggagt tctcctctat gggccccctg gatgtgctaa aaccactctg 540
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ttttcacctg ttgttggaga ttcagaaaaa gtgttgcttc agatatttcg acaagcaaga 660
gcaagcactc cagcaatttt gtttttggat gaaattgatt caatcttggg agctcgctca 720
gccagcaaga caggatgtga tgttcaagaa cgagttcttt ctgttctcct gaatgaatta 780
gatggtgttg gacttaagac aatagagaga agaggaagta aatcaagtca acaggagttt 840
caagaagttt ttaaccgaag tgtcatgatt attgcagcaa caawtagacc tgatgtgtta 900
gatactgctt tgttacgacc tgggaagatta gataagatca tctatatecc acctccagat 960
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acaaaac 1387

```

&lt;210&gt; 223

&lt;211&gt; 1506

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 223

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gaattcggca caggtgggta gaggtgatgc agtgctgaag acctgggccc ctgctcagtg 60
cctttgctct agaatgggtc cagcttggct ttggctactg ggaacagggg tcctggcctc 120
tgtccactgt cagccccctt ttgcccattg agataaaagt ctgcaggggc ctcaaccccc 180
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136

<210> 224  
 <211> 896  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (18)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (40)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (45)  
 <223> n equals a,t,g, or c

<400> 224  
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 gccaaagtcag cttcttctga gagagtctct agaagacatg atgctacact cagctttggg 180  
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 agaaatggct cagaataagt tcatcatgct aaaccttatg catgaaacca ctgataagaa 480  
 tttatcacct gatgggcaat atgtgcctag aaatcatgtt tgtagaccct tctttaacag 540  
 ttagagctga catagctgga agatactcta acagattgta cacatatgag cctcgggatt 600  
 tacccttatt gatagaaaac atgaagaaag cattaagact tattcagtca gagctataag 660  
 agatgataga aaaaagcctt cacttcaaag aagtcaaatt tcatgaagaa aacctctggc 720  
 acattgacaa atactaaatg tgcaagtata tagattttgt aatattacta tttagttttt 780  
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 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaa 896

<210> 225  
 <211> 127  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (94)  
 <223> n equals a,t,g, or c

<400> 225  
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 ctttctgact ctaagtggca ttcaaggtaa gggncatcaa aggggtacttg aatttgtaag 120



137

atgagat

127

&lt;210&gt; 226

&lt;211&gt; 1949

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1466)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1540)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 226

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attgactgcg gtaaagattt ctggggcgat gactataaaa accacgtgaa atgcataagt 360
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tttcagaatt ggatgaagaa cagtttataa gttcataatg aatccattct ggaccagggtg 600
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gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa

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1949

138

<210> 227  
<211> 1179  
<212> DNA  
<213> Homo sapiens

<400> 227  
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accatgaggg cgctggaggg gccaggcctg tcgctgctgt gcctgggtgtt ggcgctgcct 180  
gccctgctgc cggtgccggc tgtacgcgga gtggcagaaa caccaccta cccctggcgg 240  
gacgcagaga caggggagcg gctgggtgtgc gccagtgcc cccaggcac ctttgtgcag 300  
cggccgtgcc gccgagacag cccacgacg tgtggcccgt gtccaccgcg ccactacacg 360  
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gccagcagct ccagctcaga gcagtgccag cccacgcga actgcacggc cctgggcctg 660  
gccctcaatg tgccaggctc ttctctccat gacacctgt gcaccagctg cactggcttc 720  
cccctcagca ccagggtacc aggagctgag gagtgtgagc gtgccgtcat cgactttgtg 780  
gctttccagg acatctccat caagaggctg cagcggctgc tgcaggccct cgaggccccg 840  
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cataaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1179

<210> 228  
<211> 1958  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (374)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (377)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1244)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1300)

139

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1311)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1327)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 228

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gcttggtgcc ggggaagctgt gggcggtgat ttaacatgac tcaactgggg gcataggcgc 120
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gtcctgcagg ctgtaatgca gtttaatcag agtgccattt ttttttttgt tcaaattgatt 1860
ttaattattg gaatgcacaa tttttttaat atgcaaataa aaagtttaaa aacttaaaaa 1920
aaaaaaaaaa aaaaaaaagg gcggccgctc tagaggat 1958

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&lt;210&gt; 229

&lt;211&gt; 1751

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

140

<220>  
 <221> misc feature  
 <222> (1741)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1742)  
 <223> n equals a,t,g, or c

<400> 229

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cacttgaaca aacctgggtg tctttggaaa taaatcacca ttagatttca cctgggttatg 180
ctgcatccca taagttccaa atgaatcacc tgcttatcct attaacgaag catttaattc 240
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nnaaaaaggg c 1751

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<210> 230  
 <211> 2153  
 <212> DNA  
 <213> Homo sapiens

<400> 230  
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141

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ccccatattgtg gtctgtgagc cacccttaac actggttcct ttgtctcttg atatgcctac 180
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gatctgtgat ttgcaagtat tttctcccat tctgtgggtt atctttttac tttcttgata 1740
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caggagttag gaacagccta gacgacatgg taaagccccg tctctacaaa aaatagacag 1980
attagccgca tgtcgtggtg tctgcctaca gaccagcca ctcaggaggt tgaggtggca 2040
ggattgcctg agtctgggag gttaaggctg cagtgaagct tgatggagcc gctgtactcc 2100
atcctgggca acagagttag atccgagacc gtgtctcaaa aaaaaaaaaa aaa 2153

```

&lt;210&gt; 231

&lt;211&gt; 1360

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 231

```

ccacgcgtcc ggaggggagc agcctgcgca gggcaggagc agctggccca ctggcggccc 60
gcaaacactcc gtctcaccct ctggggccac tgcattctaga ggagggccgt ctgtgaggcc 120
actaccctc cagcaactgg gaggtgggac tgtcagaagc tggcccaggg tgggtggtcag 180
ctgggtcagg gacctacggc acctgctgga ccacctcgcc ttctccatcg aagcagggaa 240
gtgggagcct cgagccctcg ggtggaagct gaccccaagc cacccttcac ctggacagga 300
tgagagtgtc aggtgtgctt cgctcctggt ccctcatctt tgccatagtc acgacatgga 360
tgtttattcg aagctacatg agcttcagca tgaaaaccat ccgtctgcca cgctggctgg 420
cctcggccac caaggagatc cagggttaaaa agtacaagtg tggcctcacc aagccctgcc 480
cagccaacta ctttgcgttt aaaatctgca gtggggccgc aacgtcgtgg gccctactat 540
gtgctttgaa gaccgcatga tcatgagtcc tgtgaaaaac aatgtgggca gaggcctaaa 600

```

142

```

catcgccctgg tgaatggaac cacggggagct gtgctgggac agaaggcatt tgacatgtac 660
tctgggagatg ttatgcacct agtgaaattc cttaaagaaa ttccggggggg tgcactgggtg 720
ctggttggtc ctacgacgat ccaggggacca aaatgaacga tgaaagcagg aaactctttc 780
tgacttgggg agttcctacg caaaacaact gggcttccgg gacagctggg tcttcatagg 840
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aaacaaatac gagggatggc cagagctgct ggagatggag ggctgcatgc ccccgaagcc 960
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tgcaggctct tgccccttgt gtcgcccctt tctcctcgg aaacaaaacc ctcccacagc 1140
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atggggctct tttgtcaggg acttctgacg gctggctctg aggaaggcca aactgcccag 1260
attgagccca attaaatttt attttcttg ttttgaatac caaaaaaaaa aaaaaaaaaa 1320
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1360

```

&lt;210&gt; 232

&lt;211&gt; 1986

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (6)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 232

```

ggcacnagcg ccgcccgggcc gcagcatggg gcgcttccgc gggggcctgc ggtgcatcaa 60
gtacctgctg cttggcttca acctgctctt ctggctggct ggatcggccg tcattgcttt 120
tggactatgg ttctgggttcg gaggtgccat aaaggagtta tcatcagagg acaagtcccc 180
agagtatttc tatgtggggc tgtatgttct ggttggagcc gggggcctga tgatggccgt 240
gggggttcttc ggatgctgcg gagccatgcg ggagtcgcaa tgtgtgcttg gatcattttt 300
tacctgcctc ctggtgatat ttgctgctga agtaaccact ggagtatttg cttttatagg 360
caagggggta gctatccgac atgttcagac catgtatgaa gaggtttaca atgattacct 420
taaagacagg ggaaaaggca atgggacact catcaccttc cactcaacat ttcagtgtcg 480
tggaaaagaa agctccgaac aggtccaacc tacatgcccc aaggagcttc taggcacaa 540
gaattgcata gatgaaattg agaccataat cagtgttaag ctccagctca ttggaattgt 600
cggatttgga attgcagggtc tgacgatctt tggcatgata ttcagcatgg tctctgctg 660
tgcgatacga aactcacgag atgtgatatg aagctacttc tacatgaaaa ttgcaatcta 720
aagctttcat accaaatgac acaggagctg tctcccagct catttttaac actgaaatga 780
cattaggatc taaaataatt tgctgtcaat tgtacatttg catgagtacg tatgtttggc 840
tcattactgg tttaccctt gagtgaatgc ctgtttatga tgactgagag catattcatg 900
tgtgatctgc gtgtttctgg aatatgcttt ataccgtaat gaaatctgtt tgctgggaat 960
tcttgattct tggatatata gaagaacaac ctatttcgct cccagaaaaa aaagatcaaa 1020
gagctttcag aaactttgag aacttggcta tttagaaaaa gtgataatgg gtcaagtttc 1080
tcagactgta gccattgaaa attagatgca gagaattcag agatttcttc ttaatggaag 1140
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gggtgtaagg gtttcttggg tttttttata tacatgctct cccagaata cagtaaacca 1260
cagttttaga actaaacaca tctgtaaaac taaatatagc atggaaaatc caatttgaat 1320
aagtcatgct ttcctagaat ttaaaaaata aaaagtcttc ctctggaaag agaagtcaca 1380
cagacaatca tgtgccctat aaaagtgagt gtttatagga ctaaaaaact ttaacaact 1440
ttttaaggaa atatttttgt tcttatataa aaacatgtaa atattgcttt attactttca 1500
ttttctgacc ctgctgtaaa ctactgcaac cctcacatcc tcaaagggac ttttatgtca 1560

```

## 143

```

aactcttctg tttctccaaa tataaggaaa aaagactaaa gcaagagatc tggcagttga 1620
aaattgtggg aaagagaatt tgtatgggca ctgtatctat gaaatacctc ataacttacg 1680
tttacaatgtt ttcctaactt tttgtatttt tcttggatag ccacctagag aattcttcat 1740
agattaagaa ctacagtttt caccacttaa cataagtaaa acaaagtcct tcataattta 1800
accattagca tcttttgcca aaccctaaata aagaaaagca tcttctccta gttgtgtgtg 1860
ggcaacagaa acaagttaag gaaacccaaa tacttatata tacacaggac caaaataatg 1920
ttctttttat gcaaattcccc tgtggaaata aaattttcaa tgtttaaaaa aaaaaaaaaa 1980
aaaaaa                                     1986

```

&lt;210&gt; 233

&lt;211&gt; 705

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (108)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (680)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (696)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 233

```

ggattacatg tagttattga gaatcctttc gtaattcagt ggcttaatca tgtaatgtct 60
aaatattgtt gtacattagg atgtatacat gtaaattaaa gttacatntg tttagcatag 120
acaagcttaa cattgtagat gtttctcttc aaaaatcatc ttaaaccattt gcatttggaa 180
ttgtgttaaa tagaatgtgt gaacactgta ttagtaaaact tcatcacctt tctacttctt 240
tatagtttga acttttccagt tttttagtgg cccaacagc tgctcaattt agagcaaatt 300
aatttaacac ctgccaaaaa aaggctgctg ttggcttctc agttgtcttt aaattcaaatt 360
gctcatgtga cttttatcac atcaaaaaat atttcattaa tgattcacct ttagctctga 420
aaattaccgc gtttagtaat tatagtgggc ttataaaaac atgcaactct ttttgatagt 480
tatttgagaa ttttggtgaa aaatatttag ctgagggcag tatagaactt ataaaccaat 540
atattgatat ttttaaaaca tttttacata taagtaaact gccatctttg agcataacta 600
catttaaaaa taaagctgca tattttttaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 660
aaaaaaaaar ggggggggggn ccccaaaaaa aaccnntttt ttttt                                     705

```

&lt;210&gt; 234

&lt;211&gt; 838

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (32)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (51)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (822)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (832)

<223> n equals a,t,g, or c

<400> 234

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taaaccgaa gtgccaaata ataatttaaa anatgttaat ttttttgcc ncctaaattt 60
gccctttcca tccattaaaa atgtccaagt tccaagtgat atgtgccct aatatccacc 120
ttggatgttg gtgggttttt gaatttttgg gtgggttaatc cagttttatt ttgaaaagac 180
gtacttgaat agttacagca tatgtttgaa caggaagtag gaacatgcat acacgaagaa 240
atgctaacgg aaggatttgt tatgtttagg atcttccctt ggaaactaaa aatagaatat 300
taatgacatt actgtttgta gaatgacata tgcagatttt ctcataagca gtcatttgtt 360
ttgccagtaa tgtttgagag acatgtaagt tgaaagtttt gctaaattat aaagctcctt 420
taattcggtg gttttgattc tcttattctc ttgtcttttc taaatgttaa caaaatata 480
cttaacagat tacatgaaat ttaggaatta tttaaaagtt accattagct ctaaaattaa 540
gattcggatg ctttatttat agtaactgaa gctaataatg ttttatgttt tgattttttg 600
aaatttaatt gtagaagtca ctgccttctg agttttcaaa tagataacca cctttaatat 660
tacactgctt ataatactaa tgtttacaga tatgtttctg tttataacca tataatacat 720
tggctttgtc atattagttt tttttgcaag tagttatgta aaagagatag ataataaaat 780
attaataaac aaaaaaaaaa raaaargctc gagtaarggc anagtggcat gngccata 838

```

<210> 235

<211> 1410

<212> DNA

<213> Homo sapiens

<400> 235

```

ccacgcgtcc ggtccctagg agataagagt atcttgcaca gcagggtgcag gtttcccagc 60
agctcaggca agagtccgat gtttgtgccca tctgatcctg atgtctggag agatagccat 120
gtgtgagcct gaatttggca atgacaaggc cagggagccg agcgtgggtg gcagggtggcg 180
agtgtccttg tacgaacggt ttgtgcagcc atgtctggtc gaactgctgg gctctgctct 240
cttcactctc atcgggtgcc tgtcggctcat tgagaatggg acggacactg ggctgctgca 300
gccggccctg gccacgggc tggctttggg gctcgtgatt gccacgctgg ggaatatcag 360
tgggtggacac ttcaaccctg cgggtgtccct ggcagccatg ctgatcggag gcctcaacct 420
gggtgatgctc ctcccgtact gggcttcaca gctgctcggg gggatgctcg gggctgcctt 480
ggccaaggcg gtgagtcctg aggagaggtt ctggaatgca tctggggcgg cctttgtgac 540
agtccaggag caggggcagg tggcaggggc gttgggtggca gagatcatcc tgacgacgct 600
gctggccctg gctgtatgca tgggtgccat caatgagaag acaaagggcc ctctggcccc 660
gttctccatc ggctttgccc tcaccgtgga taccctggct gggggccctg tgtctggagg 720

```



145

```

ctgcatgaat cccgcccgtg cttttggacc tgcggtggtg gccaacccact ggaacttcca 780
ctggatctac tggctgggccc cactcctggc tggcctgctt gttggactgc tcattagggtg 840
cttcattgga gatgggaaga cccgcctcat cctgaaggct cagtgaagca gagctcgtgg 900
gattcctgct gctccagggtg tcctcagctc acctgtccca gactgaggac aggggagttc 960
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tcacagaga cccagcctg gggaacacgc tgcccgcact gccagagag cagtgcaaac 1140
accacaacac gagcgtgttt cttgagagga atgtccccga gttggacaag gaggctgttt 1200
ctgcacatca gctcatttcc cgcaccccat ttcttgcttg attgctttgt tgggggcctg 1260
gccacttcc tgccttctcaa gctgacaatt ctcaacttgc aataaatagt ccagtgtttc 1320
cttccaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1380
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa                                     1410

```

```

<210> 236
<211> 422
<212> DNA
<213> Homo sapiens

```

```

<400> 236
aaactatttta gtctgtaaca gagccatatg ctgcagggt aactcacagt agaaatgggc 60
aatttcgacg cgctgtttat ctttaccag cttcaccagg cgttcggcaa catcaattgc 120
tttctgccac tcactggtag cctggtagat ttgtagcaac tgttgacg cgccaatgcg 180
gaagtcagtt tcacgggtca gctgattgaa catgtcttcc gcgcggtcat ataaccggc 240
ggccatgtaa tcacgccccca gttgttgaat cgccaacaga cgctgttcat aggtcagcga 300
ggcgctttcc attaggtgtc gatggatgcg aatagcgcg ttcaacttcg ccacggaacg 360
ggaacagggtt ttccgagcgt aagggtgggct tcaacgggtc ccgttattec tgttttaagc 420
at                                     422

```

```

<210> 237
<211> 351
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (253)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (322)
<223> n equals a,t,g, or c

```

```

<400> 237
ctgtccctgc actccgtggc ggaaggcggc tagagcggt cctctgagc tctccgagag 60
attggctcggg acctgaagcg ttgagggttaa gggcaaggca aggagcaacg aggagttttt 120
cgttacgtta gaaaaatttc gttgctgctt gaaagcgctt ttacctgtgt tgtatgattt 180
aaccttatga aaatggacag tatttccagt tttaacaagt aggaaagaag attaagaaac 240
ttgcctccgc cangcgtggt ggttcactcc ctgtaatccc agcaacttctc gcggccgaag 300
caagcggatc acttgagggtc angagttcga agaccagcct gggccaaaca t 351

```

146

<210> 238  
<211> 2682  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (647)  
<223> n equals a,t,g, or c

<400> 238  
gaatacccca ggatttatgt ataaaaacct gcagtgtctg gttattgatg aagctgatcg 60  
tatctttgat gtgggggttg aagaggaatt aaagcaaatt attaaacttt tgccaacacg 120  
tagacagact atgctctttt ctgccacca aactcgaaaa gttgaagacc tggcaaggat 180  
ttctctgaaa aaggagccat tgtatgttgg cgttgatgat gataaagcga atgcaacagt 240  
ggatgggtctt gaacagaaga accgaaagaa gaagccttat gtcttctttt catcttgtat 300  
gtctgtgaaa taccactatg agttgctgaa ctacattgat ttgcccgctt tggccattca 360  
tggaagcaa aagcaaaata agcgtacaac cacattcttc cagttctgca atgcagattc 420  
gggaacacta ttgtgtacgg atgtggcagc gagaggacta gacattcctg aagtcgactg 480  
gattgttcag tatgaccctc cggatgaccc taaggaatat attcatcgtg tgggtagaac 540  
agccagaggc ytaaatggga gagggcatgc cttgctcatt ttgcgccag aagaattggg 600  
ttttcttcgt tacttgaaac aatccaaggt tccattaagt gaatttngac ttttctcgtt 660  
ctaaaatttc tgacattcag tctcagcttg agaaattgat tgaaaagaat tactttcttc 720  
ataagtcagc ccaggaagca tataagtcac acatacagc ctatgattcc cattctctga 780  
aacagatctt taatgttaat aacctaaatt tgcctcaggt tgctctgtca tttggtttca 840  
agggtgcctc cttcgttgat ctgaacgtca acagtaatga aggcaagcag aaaaagcgag 900  
gaggtggttg tggatttggc taccagaaaa ccaagaaagt tgagaaatcc aaaatcttta 960  
aacacattag caagaaatca tctgacagca ggcagttctc tctactgaac catgccttcc 1020  
tttcatcttg aataactttg tcctaaaatg aatttttttt ccccttgatt taacaggatt 1080  
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cactgagcac tgttacttct atcacgtctc tcttttattt ctgggatata aaacaggctt 1200  
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tatttttaatt ttaaatatcc ctccctcata caagtgtatg ttaccatttt aatataattc 1320  
tttttgtacc tttccttctt gttttgtgaa gatttttgtg gcatggattg ctgtgctcac 1380  
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gcctttgcac tctgtagagt acttagaaga caagggaac ttacttggag ttagagccaa 1920  
gctgtcagac ggtgcccagc acacattaat gttagcttct ttctgagaaa aaaatacctc 1980  
ttccaggccc tgaaacaaaa aatacatttg ctgtgaagat tgaaaatgaa caaagttaga 2040  
aaaaaaaaa gcaaaatcag tgatttagtc agatgagttt ttcgttgtag gagcacttga 2100  
tttctagtgt gttttgtaca gtatataact acaagatagt acattttgta gcagttcaaa 2160  
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agtgtgctaa catcgaatat agagaaaact ggtaaagaac attccagtag gaaaagaaaa 2280  
gaacaatctt ccatttctgg gcttggccac catcacctg gtcggacctg tcctggactt 2340  
ccaaccttga ctgctgagct cctggcttag cttcttgggt tcctaattcc tgggtgttta 2400

147

```

taattctctc caccgatcatg tttttctgat tttttttttc agaaataatg ttttttaaaa 2460
gacaaaaaca aagggaagaa tatttaatta ctgagcagaa gtaaatactg ttggtatttt 2520
gtacataatc taatttttat atgcatgtty atgcttttta atttttttat caaaaattaa 2580
gtcatctacc tactacttgt aaccagcttg tttcataaca tggtattttc ctgtgtcatt 2640
aaataattac ttcaatgttg aaaaaaaaaa aaaaaaaaaa aa 2682

```

&lt;210&gt; 239

&lt;211&gt; 2254

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 239

```

gataatattt aatgttggtc tgcacatctc tatacagtta actttttggc tttcattctg 60
tatagataag aaaatgttat attataaaca gcctactcag tgcaaatatt tatctgttta 120
tcaaattccac aatatgctgt ataataccgg ttttactata taatctattt tagacatagc 180
tgtttagaac tagagtgtgc tatttttgtg tttttctgat gtgtgggtgct agacaagtta 240
cttttgtgaa caacaaaaat tatccctttt attcctagac aataccacct ttgggtcttg 300
ttaatttcac tgagtataac tataatattg tatatatata catatatata tatatctacc 360
tatgccaac tggcagctgt atcagagtgc tggatttggg acatgctttt ctctttaaat 420
acataatatc attatataaa ttattctaga gtgtatttaa ttaggataaa attacttcct 480
tagtatggat atttgacatc tatagggtga atttgtttat aaatatggct atatggaaac 540
ttattagcat ttactttatg tttgctactt ggctttacag catatctcct aagctgaaaa 600
ataatttgcc aggccctcaa gatcctaaag aaacttgttt aatggagtaa tatacttttt 660
tttcttatta aggaattgta ttactggcac ctaacacagt tgtattctta gctcctatta 720
tagataatgg gcatttacat aaaatatact agatggcttg atggcagaat aaacctttcc 780
cctcctacct gagtcatgag aaggatggag acgtcctctg ccataacatg ggccataaag 840
caaatctgac atgggatgtt ctgtttcagt atgacctcaa ccagttccat gaactgagtg 900
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tcccaagatc tattggcatt attgaaaagc aaagtttatc aaatatctaa ctaaggatgt 1020
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tttagcaaag atttttgagc aattttataaa tgtagagcaa atgtttctgt ttactgcaat 1140
ttttgtaact gaaggtgata aattctcaag ccatgattat tggcttccat gcaactgcaat 1200
atttatccac aattctagac attttccatt tttgtggaag agttgctgtt accttaatta 1260
taaatgcaat tgtgtggtta atgagagcta atgctagtag ttaacctttt aaagtggatt 1320
ggctacagtt gagggagaaa tctcttttaa tataaatcac atcattcctt aactgcctct 1380
cttggaaga gattgaaacc ttttttttaa agcagattt agcaccctaa gcttcctgag 1440
ggtagagatt gtatcttttt gcgtctgcac aatggctagc acatgtcagc atttgacaat 1500
tgtaaataga taacaagtgt gccccaatta aaacgttttt cctgggttgt tttgttaaata 1560
ttacaaagta agccaagcct tacgggttaac attctcctct acaaccaagt attaaagcca 1620
catttaaaaa gaccacatga aatgctgatt ctaatttgtt gtaggtcttg aggattaagc 1680
acacaaattt cacaaacttc tgtttgagta aacaaactca gccttctgta aatatacatg 1740
caagtttgga aacagtaata ctgtacctat aaatatatgc tgtctgtttt gtgtacagta 1800
tgtaaaaact ctttttctgc cactactaaa atgcaagcca tttatgggaa tcctaaaact 1860
agtattgaac taaaactttg ctaatgatct ttattagagg atcgtccaac ttttcactta 1920
ccytgggttt tcttttcaat tcactcttac actagtctgc ttatttccag ctgtttattt 1980
tattgagtcc tgaattttaa aaaaaaatat tttgattcat tttgtaaata caagctgtac 2040
aaaaaagaga gatttaatgt tgtcttttaa atactccaat tttcattcta atatgaatgt 2100
tgttatatgt tacttagaaa ctgtaccttt aatattacat tacctttatt aaaagtgcac 2160
tgaacacatc aatttttagat gtgctttatg tactgttata ctataataaa acttcagctt 2220
ctaattggaa aaaaaaaaaa aaaaaaaact cgag 2254

```

148

<210> 240  
 <211> 1057  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (958)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (966)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1035)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1053)  
 <223> n equals a,t,g, or c

<400> 240  
 ttaactcaaa ctctaaagtc ttgagtgttt caaagtcagt cgttacctgt ttaaaagcct 60  
 cagccttttag cttattcctc cttcaataca cgggaccttt ggtaatttg gggcaggaaa 120  
 actcttaaag taatctctct tgggcagagg cttatttgca ccagaggga aaagtatata 180  
 cttcatttgc tgttactcca gttatgcctt aaattcattt gcttggtaat cctatcaacg 240  
 rgcactaact tcttagtata ctttaaacac ttagttgggt aacactgaga ttttggtgtc 300  
 ctttattttt tgctgagatg gagtcagtca gatgttagtc atagctaaca ccgaatttgt 360  
 gttgtcattt agacagttac tgattcgatc tgctttatat atgagaacgt atttttaact 420  
 attccaagaa ggaagaggta gctaaatgta atcccccttt cctatcccc cagaaaactg 480  
 aactgtaagt tctaggtaga ctaattggga gcagacacgg agtttttagat gccttagcca 540  
 aaccagcag aaacctttca cacagccact catcgtaaga aacgcagatt tttctcttct 600  
 catgcttgtc tctggttccc tgcatttcta gtgacagaac tttcactagc aggatataaa 660  
 gaaagtaatt atgcttggag tccctcttta ctgggtttga gttaggtgca taacatggaa 720  
 aggagtgggt ccttcaaagt aatgtgacca ctccgtattg tggagtgact tccctagggc 780  
 atcctataca tcctaccaca gaaggccaag ggacagagca ccaacttcag tatccaagaa 840  
 attagatcca caactcttga ttttccacac tgaggactgt cgcgagtaag ttgtaagttt 900  
 gccgtcttcc ttctggctta gcaggtgctg cagctgtact ctcgactcct gtctgtgnag 960  
 cgtganyagg gaaaatgagg agtggagtct atttccaaaa aaaaatgtgg atggagtttt 1020  
 ttccttaaag tggcnttcat tggcccaatt ccntttt 1057

<210> 241  
 <211> 498  
 <212> DNA  
 <213> Homo sapiens

<220>

149

<221> misc feature  
 <222> (493)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (496)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (497)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (498)  
 <223> n equals a,t,g, or c

<400> 241  
 gagttgatcc tgagatgaag gtggagcgtt acaagcgcac ctttgaccaa aatgaggagc 60  
 taggggtcaa tgacatgaag acagagggct atgaggcagg cctgggtccg caacggtagc 120  
 agtgggtggc tcaagggcca gcctccagcg ctgctctttc tgtaggttat ttattagtat 180  
 tggatgaagg cgaaggctgg gagtgtcttt cccaccagcc cttgcccatt gtggggagga 240  
 catctggtct gagtcagaga tctgtgcaca ctttctaaac agcttgtgat gcaagtgtga 300  
 gcctattgtg ttacttgacc ttattttgga agttttgaat tggcctagga ggaaacccag 360  
 aaatgaacca ggggtatgtc atcacttttt tcatatcaag tcctcaccct ccttccacat 420  
 aatgctctat cctctaargt tggaactctg aarttggaaga argtggaata aagttacacc 480  
 tggaaaaaaa aanaannn 498

<210> 242  
 <211> 1784  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (1739)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1777)  
 <223> n equals a,t,g, or c

<400> 242  
 ggcacgagcc aacccagcta tggcctatgc caacgaggtg aaacgtgtgg tcagcagtg 60  
 acaggagaag ggcaggaaga ttgcagcctt cttcgtgag tctctgccc gtgtgggagg 120  
 gcagatcatt cccctgctg gctacttctc ccaagtggca gagcacatcc gcaaggcccg 180  
 aggggtcttt gttgcmgat agatccaggt tggctttggc cgggtaggca agcacttctg 240  
 ggccttccag ctccagggaa aagacttcgt ccctgacatc gtcaccatgg gcaagtccat 300

150

```

tggcaacggc caccctgttg cctgcgtggc cgcaaccag cctgtggcga gggcatttga 360
agccaccggg ttgagtactt caacacgttt gggggcagcc cagtgtcctg cgctgtgggg 420
ctggccgtcc tgaatgtctt ggagaaggag cagcyccagg atcatgccac cagtgtaggc 480
agcttcctga tgcagctcct cgggcagcaa aaaatcaaac atcccatcgt cggggatgtc 540
aggggtgttg ggctcttcat tgggtgtggat ctgatcaaag atgaggccac aaggacacca 600
gcaactgaag aggtgycta cttggtatca aggtgaagg agaactacgt ttgctgagc 660
actgatggcc ctgggaggaa matcctgaag tttaagcccc caatgtgctt cagcctggac 720
aatgcacggc aggtggtggc aaagctggat gccattctga ctgacatgga agagaagggtg 780
agaagtgttg aaacgctgag gctccagccc taagccagcc ctgctctgcc taagtgtact 840
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ttacagataa agtcagcttt cagaggtcga ggggtggggg gcctgcccga ggccataatg 960
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tcaagtcagt caatttcctt tctgtccact gggggtggaa tggggtaggg tgggatactt 1080
taaagtgttc ctgcttaaat aaattagacc agaccagtgt atttctaaag aaaatcctga 1140
catgcacacc cattaataat agtacatttt acagtgtccc agtcatactt ttaattggca 1200
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cactggagta ataaccactg ctccccctaa ctgcctcaaa gactgtcatt ttatagaaaa 1440
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ttccacctgt cccacettat ctggtgcca actcctgctc agaaacagaa cctgccacac 1560
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ttgaaagcac aactgacctt ggatttaagc tggccaggac cctgggagat ctttggaang 1740
atTTTTgcct gggtttaagg ttaacttaaa gaggtgncca gaag 1784

```

&lt;210&gt; 243

&lt;211&gt; 936

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (840)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (854)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (865)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (905)

&lt;223&gt; n equals a,t,g, or c

## 151

&lt;400&gt; 243

```

catatgtttg cttgggatag aggtcaaaga ggatcctctg gcatgttttg ctgggttcct 60
gtagtcatTT caacaggatt aactataatc tataattgat agattattga gtgacacaca 120
gCGTgatgct gggcaggccc caagctgaaa agcatctcct ccaacttact ttattcttag 180
caattcattc ctttggtttg aaaattcttc agcatcttca agagtccttt actaatgsat 240
cctttggggg agttgtgcta aattatcaac tcacaaggat gagatkgctg gctctaggga 300
gccagcctgc caacatggat gggctgtccc aggstctcaa gtgagctcag gtctgtacac 360
tgcactccrg ggagagtaaa tgtgcctggg gcatagaatg gagactttgg agtttggagt 420
ttggagtggg tttggggaca tcagcttctc tcttccagtt agtctgataa gtcctttgtt 480
gcctggccct ggaaaccact tgtscctccga aaatgccatt ctctggaatg tagctgtgga 540
gtagggagag agttggcccc tgtgttctgt aacccaagca agtactgtct cactgccatc 600
ttggggcgaga ctccgcagta aggagaatct ctcttgccct tttgtgtttc ttggtttctt 660
cctttgtaaa tacaaggcat agtctctgcc cttcccccag attgccagaa gagtgggata 720
tattgttcta gcaatataaa gctctgaggc ctttctgcag gactgtagac accactttgc 780
tgtgatagtg aagaatgtgg gggagtgttg tgagggctag gcgaagcggc ccggccttgn 840
ccattgaca gctncagtct tcctncctc ataactttt taacctaaca gaggatttaa 900
aaaanaaaaa caatttttagc tggggcacaa tggctc 936

```

&lt;210&gt; 244

&lt;211&gt; 1381

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1348)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1349)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1350)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1358)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1359)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 244

```

tccgtgggtgt ggttgactct gaggatctgc ccttgaacat ctcccagaaa atgctccagc 60
agagcaaaat cttgaaagtc attcgcaaaa acattgttaa gaagtgcctt gagctcttct 120

```

152

```

ctgagctggc agaagacaag gagaattaca agaaattcta tgaggcattc tctaaaaatc 180
tcaagcttgg aatccacgaa gactccacta accgccgccg cctgtctgag ctgctgcgct 240
atcatacctc ccagtctgga gatgagatga catctctgtc agagtatgtt tctcgcata 300
aggagacaca gaagtccatc tattacatca ctggtgagag caaagagcag gtggccaact 360
cagcttttgt ggagcgcagt cggaacggg gcttcgaggt ggtatatatg accgagccca 420
ttgacgagta ctgtgtgcag cagctcaagg aatttgatgg gaagagcctg gtctcagtta 480
ccaaggaggg tctggagctg cctgaggatg aggaggagaa gaagaagatg gaagagagca 540
aggcaaagtt tgagaacctc tgcaagctca tgaaagaaat cttagataag aaggttgaga 600
aggtgacaat ctccaataga cttgtgtctt caccttgctg cattgtgacc agcacctacg 660
gctggacagc caatatggag cggatcatga aagcccaggc acttcgggac aactccacca 720
tgggctatat gatggccaaa aagcacctgg agatcaaccc tgaccacccc attgtggaga 780
cgctgcggca gaaggtctgag gccgacaaga atgataaggc agttaaggac ctggtggtgc 840
tgctgtttga aaccgccctg ctatcttctg gcttttccct tgaggatccc cagaccact 900
ccaaccgcat ctatcgcagt atcaagctag gtctaggtat tgatgaagat gaagtggcag 960
cagaggaacc caatgctgca gttcctgatg agatccccc tctcgagggc gatgaggatg 1020
cgtctcgcag ggaagaagtc gattaggtta ggagttcata gttggaaaac ttgtgccctt 1080
gtatagtgtc cccatgggct cccactgcag cctcgagtgc ccctgtccca cctggctccc 1140
cctgctggtg tctagtgttt ttttccctct cctgtccttg tgttgaaggc agtaaaactaa 1200
gggtgtcaag cccattccc tctctactct tgacagcagg attggatgtt gtgtattgtg 1260
gtttatttta ttttcttcat tttgttctga aattaaagta tgcaaaataa agaatatgcc 1320
gtttttatata aaaaaaaaaa aaaaaaannn gggggggngg ccccggtccc matttcccc 1380
c

```

&lt;210&gt; 245

&lt;211&gt; 779

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (10)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (39)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (41)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (650)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (669)



153

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 245

```

cttttccttn caggtggaaa ggaccccttg gtacccatnc ncaagcagtt aggaaaggac 60
ctggctcttt acatatattg gatggtcctc atggcaaaac ttctcaattc ctttaattagt 120
catgtctcag cttcaaggat atcagacagg aatgaaacac acttgaaaat gagattgacc 180
tggagatttt ttttccctaa tctctcatac ctttaattgga aaaataatca attaattcta 240
tgtaatttag grtatacaaaa gttcacccctc cttgmaagtg actagggcaa gccctgaaga 300
tcttcctcac ctcccttttat ctttctataa ccttgtctcc tccagcacca cagggaagac 360
aatcacagtg ggtcaagagc gaccctcttt cactgaggct ctgcatgacc tctgagacct 420
gcttatgatc agtgcaatga agttagaagt aactgatgat tgggagcctt tgcagatagc 480
tgggcaaatg ggtgatttac ttatcccat tctaaatgga gtgagctctc tttgaggcta 540
agcaaggagg cgttgtatgc tagtttctag actttgcctg gagaccctt tggaaatctg 600
tcttcttttt aaactcactt aatatgcctt aatcatctgk gtgtaatggn agtcatccgc 660
tcctcaatnt aaccctyctm ccctggggct ttggctgtcc tcaatgagag tttcatgcag 720
aatggaaaat cctctatatg tacaatctct ctcccectca tttctcttcc tcctcacct 779

```

&lt;210&gt; 246

&lt;211&gt; 1231

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (795)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1219)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1229)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1230)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1231)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 246

```

ccacgcgtcc ggaagaaggc ctaattccta acctgggacc cagagagaga cataagatat 60
ccagagagat atgcaccaag aaactgcaat ttatacaaag acagtcagaa agcagctgaa 120
gacagaatga gagagaaact aagtaaaaga aacttgatgc ctccaaaatg aagagtatgc 180

```

154

```

ctcatttcca tatgtgaact gaaaagctct ccacttttga aataaaggct tactatagag 240
cagccctggg aatagaacta caagacttat aataacttcc tgtttgagtt gaaatgaaaa 300
ctcataaaga atctatgcta ttaaccccct aatttatact tttgtattct tttatgttgt 360
attttgtatt ttatgttgga cttctttttt aaaattttgt atttattttt aattgaaaaa 420
taattgtgta tacttattgt tgtacaacat gatgttttga tatatgtata tgttgtagaa 480
tgactaaatc aagctagtta acatatgcat tacctcctat acttatcatt tatttgtggg 540
gagaacatctt aaaatctact ctgttagcaa ttttgaagta tagaatacac tatgtcaact 600
ataatcatgg tgttgtacag taggtctaaa tgtattcatt tctcctatct aactgaaaat 660
ttgtatcttt tgaccaacat ctccctgggc cctccatctc ctcccctggg aactaccatt 720
attttttttt ctttttttta aaaaaaagct tttagtttcg aggggtacacg tgtaggtttg 780
ttatatagat aaacncaagt catgggactg tgttgtacag attattttgt cgtccacgta 840
ctaagcctag tgcccaatag ttattttttc tgctcttctc cctcctccta ccctctgcca 900
tcaagttggc ctaatgtcta ttgttccctt ctttgtaaca accactctaa tctctgcttc 960
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tgcagcagta gtttatttat ttccattatt ggatagttatt cctttgtgtg aacataaatt 1080
gctgatggca gatgtttgaa ttgtttccag tttttgagta ttatgaataa tgctgttgtg 1140
aacaaaaaaa aaaaaaaaaa aaaaaaaggc cggccgctct agaggatcca agcttgcgta 1200
cgcggtgcag aaacgtcana aggggtctnn n 1231

```

&lt;210&gt; 247

&lt;211&gt; 851

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (817)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (834)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (842)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (844)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (849)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 247

gcggacgcgt gggcgtggat cggctggagc ggggcccgcg ccggctgcag caggagctgg 60

155

```

acgacgccac catggacctg gagcagcagc ggcagcttgt gagcaccctg gagaagaagc 120
agcgcaagtt tgaccagctt ctggcagagg agaaggcagc tgtacttcgg gcagtggagg 180
aacgtgagcg ggccgaggca gagggccggg agcgtgaggc tcgggccctg tcaactgacac 240
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ggaacgagcc tgccgggtag cagaacaggc agccaatgat ctgcgagcac aggtgacaga 420
actggaggat gagctgacag cggccgagga tgccaagctg cgtctggagg tgactgtgca 480
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gcgagggcag ctggccaagc agctgagaga tgcagagggtg gagcgggatg aggagcggaa 600
gcagcgcaact ctggccgtgg ctgcccgcaa gaagctggag ggagagctgg aggagctgaa 660
ggctcagatg gcctctgccg gccagggcaa ggaggaggcg gtgaagcagc ttcgcaagat 720
gcaggccccag atgaaggagc tatggcgggg ggtggaggag acacgcacct tccgggagga 780
gatcttctcc cagaatcggg aaagtgaata gcgcctnaag ggctgaagc tgaagtgtctg 840
cngntgcang a 851

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&lt;210&gt; 248

&lt;211&gt; 1802

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1680)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1747)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1757)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1800)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 248

```

acgcgtccgc ttccatctgc tctggaatta aatatgcatt tcagggtgatt ggagagctac 60
attcccaact cgatggatcc gaagtactgc tgctgactga tggggaggat aacactgcaa 120
gttcttgtat tgatgaagtg aaacaaagtg gggccattgt tcattttatt gctttgggaa 180
gagctgctga tgaagcagta atagagatga gcaagataac aggaggaagt catttttatg 240
tttcagatga agctcagaac aatggcctca ttgatgcttt tggggctytt acatcaggaa 300
atactgatct ctccsagaag tcccttcagc tcgaaagtaa gggattaaca ctgaatagta 360
atgcctggat gaacgacact gtcataattg atagtacagt gggaaaggac acgttctttc 420
tcatcacatg gaacagtctg cctcccagta tttctctytg ggatcccagt ggaacaataa 480
tggaaaattt cacagtggat gcaacttcca aaatggccta tctyagtatt ccaggaactg 540
saaaggtggg cacttgggca tacaatctty aagccaaagc gamcccagaa acmttaacta 600

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## 156

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ttacagtwac ttctcgagca kcaaaattct tctgtgcctc caatcacagt gaatgctaaa 660
atgaataagg acgtaaacag tttccccagc ccaatgattg tttacgcaga aattctacaa 720
ggatatgtac ctgttcttgg agccaatgtg actgctttca ttgaatcaca gaatggacat 780
acagaagttt tggaactttt ggataatggg gcaggcgctg attctttcaa gaatgatgga 840
gtctactcca ggtattttac agcatatata gaaaatggca gatatagctt aaaagttcgg 900
gctcatggag gagcaaacac tgccaggcta aaattacggc ctccactgaa tagagccgcg 960
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gatgaggata ctcagaccac cttggaggat ttcagccgaa cagcatccgg aggtkcattt 1080
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taagagacag ttttgatgat gctcttcaag taaatactac tgatctgtca ccaaaggagg 1320
ccaactccaa ggaaagcttt gcatttaaac cagaaaatat ctcagaagaa aatgcaaccc 1380
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ctcctactcc tactcctgat aaaagtcata attctggagt taatatttct acgctgggat 1560
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aagtaaagga tatttctgaa tcttaaaatt catcccatgt gtgatcataa actcataaaa 1740
ataattntaa gatgtcngga aaaggatact ttgattaaaa taaaaacact catggatatn 1800
ta 1802

```

&lt;210&gt; 249

&lt;211&gt; 444

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 249

```

gggtgccttt ctcatggcca cagcagcttg gcttacaacc gtcttcaaac agccaggctg 60
tgccccagaa ctccactggg cttccttcca taactatgga tctgtgagca tcactttaat 120
ttcagagtgt ggaagacacc ttaataagaa tcatgaatca cattttacaa atcaggatac 180
acaggatgta aggttaagtg acctgtccta tcaggggccac aaagccagtt aaacttcttt 240
attaactgag tcacttaaaa atcatttatt taaaaacctt ttttgttcca ggaactattc 300
tgggtactgg aaatraaaac agtggagaca gagagagggg aaatpaaaaa caagacaaaa 360
atgattgctt tkggtggagt tatatattcc actggargaa ggtagatsat aaataaaagt 420
gaaaaagtac attatwaggt ggga 444

```

&lt;210&gt; 250

&lt;211&gt; 1746

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 250

```

ggcatcagta aggtctgtat ttaaattgtg atgtagacat cataattacc aagacaagaa 60
attgttttga gaaattctct gatgtttttc ttcttcaggt ttcacgtgcc acgatcatgg 120
tgccacggta ctgcagtatg caccctaaaca gcaactccta atctcggggg gtaggaaaaag 180
acacgtctgc atttttgaca tcargcaaag gcagctcatt cacacgttcc aggcccatga 240
ctcagctatt aaggctctgg ccttgatcc ctatgaggaa tattttacca caggttcagc 300
agaaggtaac ataaagggtt ggagattgac aggccatggc ctaattcatt catttaaaag 360
tgaacatgct aagcagttca tatttcgaaa cattggggct ggagtcatgc agattgacat 420
catccagggc aatcggctct tctcctgtgg tgcagatggc acgctgaaaa ccagggtttt 480

```

157

```

gcccaatgct ttttaacatcc ctaacagaat tcttgacatt ctataaagat tgggggtttta 540
tttttatata catttcagtt aaaaggcaca ctacagtcac cactaggcaa ttctgctttc 600
taagcagttg tattgaaaac agagaatctc tgtgtagaat ttgaatatga cccaagctga 660
gtattatcta aacaggttgg tggaatgaat gcgcattgtac cttattatgc tgacatacta 720
aaaaaaataa aacctagtat tgtatgaagg atagctattc tttacagcat ttagcaaac 780
tgattcagaa aacattttgag attagcaaat tagtaacttg aaataatgaa aaggacgttt 840
ataccaaaatt aaggaagaaa atgttgctga tttgggtttt tcttcctgtt cttaccactg 900
actgaagcat gcctgcagtc tctcctctg ttgaatgaag gataatcata aggtgtttgt 960
taggagcgct agaccacctg gaaaactttc ttagctgtgg agcagtgcgc agtgaccagt 1020
tctctgctgt gagaggccgt ttccattctt tctgctgaa tatttttcct gttagtgttt 1080
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gttaggaatg tactatgtga acatgacata tttgtagtta accaaacaca cttctcttagt 1260
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tgttgaaact acaccaatag agcatttcat atcataatta aaatgaatgt taggcttctt 1380
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aactatgcag agttaaatat ttgcttgtaa aatattagcc aatgttgtca ttattttgat 1500
gtatttcctt ggttatgacc aaaaatatgt tgagatactg aaactaatgt ctgtgtgttt 1560
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aatagtaaat acaatggcat aaaagtaact ttctctgaag atgtgatgtt caggctgtga 1680
aatatatatg taaaagaaaa ataatgtta tttgttagaa aaaaaaaaaa aaaaaaaaaa 1740
ctcgta 1746

```

&lt;210&gt; 251

&lt;211&gt; 1935

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 251

```

gaattcggca cgagggagca ttgcccgtca gacagcaact cagagaataa ccagagaaca 60
accagattga aacaatggag gatctttgtg tggcaaacac actctttgcc ctcaatttat 120
tcaagcatct ggcaaaagca agccccaccc agaacctctt cctctcccca tggagcatct 180
cgtccaccat ggccatggtc tacatgggct ccaggggcag caccgaagac cagatggcca 240
aggtgcttca gtttaatgaa gtgggagcca atgcagttac ccccatgact ccagagaact 300
ttaccagctg tgggttcattg cagcagatcc agaagggtag ttatcctgat gcgattttgc 360
aggcacaagc tgcagataaa atccattcat ctttcgcgtc tctcagctct gcaatcaatg 420
catccacagg gaattattta ctggaaagtg tcaataagct gtttggtgag aagtctgcga 480
gcttccggga agaatatatt cgactctgtc agaaatatta ctctcagaa cccagggcag 540
tagacttcct agaatgtgca gaagaagcta gaaaaaagat taattcctgg gtcaagactc 600
aaaccaaagg caaaatccca aacttgttac ctgaagggtc tgtagatggg gataccagga 660
tggtctcggg gaatgctgtc tacttcaaag gaaagtggaa aactccattt gagaagaaac 720
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## 158

```

aaaactaagc gtgctgcttc tgcaaaagat tttttagat gagctgtgtg cctcagaatt 1380
gctattttcaa attgccaaaa atttagagat gttttctaca tattttctgct cttctgaaca 1440
acttctgcta cccactaaat aaaaacacag aaataattag acaattgtct attataacat 1500
gacaacccta ttaatcattt ggtcttctaa aatgggatca tgcccattta gattttcctt 1560
actatcagtt tatttttata acattaactt ttactttggt atttattatt ttatataatg 1620
gtgagttttt aaattattgc tcaactgccta tttaatgtag ctaataaagt tatagaagca 1680
gatgatctgt taatttccta tctaataaat gcctttaatt gttctcataa tgaagaataa 1740
gtaggatatcc ctccatgccc ttctgtaata aatatctgga aaaaacatta aacaataggc 1800
aaatatatgt tatgtgcatt tctagaaata cataacacat atatatgtct gtatcttata 1860
ttcaattgca agtatataat aaataaacct gcttccaaac aacaaaaaaaa aaaaaaaaaa 1920
aactttgagg gggggg                                     1935

```

&lt;210&gt; 252

&lt;211&gt; 1919

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (253)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 252

```

ataaggcggc atttatcatt cccaccactg acatctactg tataccacat ctgctatgcc 60
atggatacat ggcatacatga tgatgagtc cccccctggg cctgccaaagg ggaaacagag 120
tgcatatccc accataatag ggaaattaat aattgtatta agtgggtgaa aaaaaggggg 180
aggatgtttca ctcaactgttc cctgtgtagt atcctgcaaa tgcatgaatg gtgaactccc 240
catgtcagca ttnttgtgcc catttattta gtaccagac atagtgtctg tctcacagct 300
taatatttgg taatgaataa attctgctag tggatatgt tgatctgaac ttacaatgat 360
gggatattaga attggcagag tggcagatgt tcacaattgt ctacaagtag atgtgctaga 420
caatggaagg atgcaggcca acctctttga ttacaattga gattcatgtg actattgagc 480
cctggaaatg tagcttgtcc aaattgagat gtgctgtcag tataaaatac ataccagatt 540
ttaaagatgt accaaaaaat gtaactatc tcaattttta tattggtgaa atcaatatgt 600
cttggatatag tggcttaaat aaaacaattt tagcctttct cagtttattt ttctgcaaaa 660
agattaaaaa ttgtacatga agctcatgtt aactttcttt tggtcagtgc tattttaaag 720
gaagtatgag ttgaaaaaaa attgaaataa actatatcat attactagga cttaatatag 780
tggcataccc aggaaatgct tagtaagtgt tcccttcaca ttttaaaatt tgagtataca 840
atcatgtttg acaatataga aatttaattt ttagtgaaac aattctaaac cccttttcca 900
tagacacaag aaagatggca aatttatgct attcctggaa aaatacattg tggcttagca 960
aataagcaag ttcccacgtt acttttgttt tgcttcaagt aatacttctg ccagttgtgt 1020
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gttggtggaa gagcagcatt ttgacccttg gagaagaaaa actagctgtg gcattccagg 1560
tggagaacct gacagaggac taagaagtta tctaagttaa aagacctcag gcaccacctt 1620
cgcataaact ttttccagac aaggctaaat gtgcatgctt cataaccata attcttattt 1680

```

## 159

```

ttctttaata aatatttttc tacttgtaac actgtgcatt atttcaaact gtttacctgt 1740
ttgtaaagct tgtctcttaa tcaaatttgt cttgaccaa taagtttcct gagggctgga 1800
attatgcctt aactatatct atagtattta acagtgaatc ctttgtataa tgaaagcatc 1860
aacagataat tttaaattga taaataaaaa gcacagtttc aaatggtaaa aaaaaaaaaa 1919

```

<210> 253

<211> 2468

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2076)

<223> n equals a,t,g, or c

<400> 253

```

gggttttgaga agattggaca gtgcttcagg caccgtgtac acagcaatgg atgtggccac 60
aggacaggag gtggccatta agcagatgaa tcttcagcag cagcccaaga aagagctgat 120
tattaatgag atcctggtca tgagggaaaa caagaaccca aacattgtga attacttgga 180
cagttacctc gtgggagatg agctgtgggt tgttatggaa tacttggtctg gaggtctcct 240
gacagatgtg gtgacagaaa cttgcatgga tgaaggccaa attgcagctg tgtgccgtga 300
gtktctgcag gctctggagt tcttgcatte gaaccagata accccagagc agagcaaacg 360
gagcaccatg gtaggaaccc catactggat ggcaccagag gttgtgacac gaaaggccta 420
tgggcccagg gttgacatct ggtccctggg catcatggcc atcgaaatga ttgaagggga 480
gcctccatac ctcaatgaaa accctctgag agccttgtac ctcatlgcca ccaatgggac 540
cccagaactt cagaacccag agaagctgtc agctatcttc cgggactttc tgaaccgctg 600
tctcgagatg gatgtggaga agagaggttc agctaaagag ctgctacagc atcaattcct 660
gaagattgcc aagccctctt ccagcctcac tccactgatt gctgcagcta aggaggcaac 720
aaagaacaat cactaaaacc aactcacc cagcctcatt gtgccaaaggc ttctgtgaga 780
taaatgcaca tttcagaaat tccaactcct gatgccctct tctccttgcc ttgcttctcc 840
catttcctga tctagcactc ctcaagactt tgatccttgg aaaccgtgtg tccagcattg 900
aagagaactg caactgaatg actaatcaga tgatggccat ttctaaataa ggaatttcct 960
cccaattcat ggatatgagg gtggtttatg attaaggggt tatataaata aatgtttcta 1020
gtcttccgtg tgtcaaaatc ctcacctcct tcataaccat ctcccacaat taattcttga 1080
ctatataaat ttatggtttg ataataattat caatttgtaa tcaattgaga tttcttttagt 1140
gcttgctttt ctgtgactca actgcccaga cacctcattg tacttgaaaa ctggaacagc 1200
ttgggaatgc catgggggtt gataatctgc cagggacatg aagaggctca gcttctctgga 1260
ccatgacttt ggctcagctg atcctgacat gggagaacaa ccacattttt ctttgtgtgt 1320
gcttctagca gctgttcggg aggaccttga cccaayagtg ttcccatgct gtttcttctgt 1380
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gttgagaagt cggggaaaat ggtgactact tttagagcaa ggctgggcat cagcacctgt 1560
ccagctctac ttgtgtgatg tttcaggaac tcagccctt tttctgccta ggataaggag 1620
ctgaaagatt aacttggtatc ttctaattgt ccaaactctt tggtcacaa aaagagtctc 1680
caaattagag actgcatgtt agttctggat ggatttgggt gcctgacatg ataccctgcc 1740
agctgtgagg ggaccccgtt tttaagatgc atggccaagc tctctgcaaa tggaaatgct 1800
tacactgggt gttggggatg tttgctacct cctgctattt ttgtggtttt ggttctccca 1860
ctatggtagg acccctggcc agcattgtgg cttgtcatgt cagccccatt gactaccttc 1920
tcatgctctg aggtactact gcctctgcag caciaatttc tatttctgtc aataaaagga 1980
gatgaaaata ttctatttga gtatgccttt cttttttctc ttcgtttttt ctttctcttt 2040
ctaatttttt atatgaaata atgagtaagt ttcttntctg accatttgag agtggttaagt 2100

```

## 160

```

tgcagataga atgccccctt accactatat acctgaatgt gtattctttc yttttaaacac 2160
ttttatttta aatataaatt aagagaaatg ggccaaaacc atttgatttg tttaaagaat 2220
aattataaac acacttgat ccaccaaatac aagaaakgga aactgacag taagaacctt 2280
ctctatcttg tccttccttt ctcatatag ccccccaccta agaggtaacc accatcttga 2340
ctttatttta aataactttc ttgcttttct gtatactttc atcacattca ggtgtgttcc 2400
aatacaagta gatttttagtt cggccagttt ttgaacttta aataaacata tcataataga 2460
taaaaaaa
2468

```

&lt;210&gt; 254

&lt;211&gt; 2861

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2861)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 254

```

ggcacarcca cagcttctcc agtggctatg tggagatgga gtttgagttt gaccggctga 60
gggccttcca ggctatgcag gtccactgta acaacatgca cacgctggga gccgctctgc 120
ctggcggggt ggaatgtcgc ttccggcgtg gccctgccat ggccctgggag ggggagccca 180
tgcgccacaa cctagggggc aacctggggg accccagagc cgggctgtc tcagtgtccc 240
ttggcgggcg tgtggctcgc tttctgcagt gccgcttctt ctttgcgggg ccctgggtac 300
tcttcagcga aatctccttc atctctgatg tggatgaaca ttctctctcg gcaactgggag 360
gcaccttccc gccagcccc tggtggccgc ctggccacc tcccaccaac ttcagcagct 420
tggagctgga gccagaggc cagcagccc tgccaaggc cgaggggagc ccgaccgcca 480
tctcatcgg ctgcctgggt gccatcatcc tgcctctgct gctcatcatt gccctcatgc 540
tctggcggtc gcaactgggc aggytctca gcaaggytga acggagggtg ttggaagagg 600
agctgacggt tcacctctct gtccctgggg aactatctt catcaacaac cggccaggtc 660
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cctgtgtccc caatggctct gcgttgctgc tctccaatcc agcctaccgc ctccttcttg 780
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agggcgctac cgggggcaac acctatgctg tgccctgact gccccaggg gcagtcgggg 1020
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agggccagtt tggggagggt cacctgtgtg aggtcgacag cctcaagat ctggtcagtc 1140
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tggaggacaa ggagccgag ggggccccct gggaggggca ggctgcgcag gggccacca 1440
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tcaccatcaa aatgcagac tttggcatga gccggaacct ctatgctggg gactattacc 1620
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aggcytatat gagctgatgc ttcggtgctg gagccgggag tctgagcagc gaccaccctt 1920

```



161

```

ttcccagctg catcggttcc tggcagagga tgcactcaac acggtgtgaa tcacacatcc 1980
agctgccccct ccctcagggg gcgatccagg ggaagccagt gacactaaaa caagaggaca 2040
caatggcacc tctgcccttc ccctcccgac agcccatcac ctctaataga ggcagtgaga 2100
ctgcaggtgg gctgggcccc cccagggagc tgatgccccct tctccccctc ctggacacac 2160
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taatcacttg gggtttgtag atttttgggg ggagagacac agatttttac actaatatat 2760
ggacctagct tgaggcaatt ttaatcccct gcactaggca ggtaataata aaggttgagt 2820
tttccacaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa n 2861

```

&lt;210&gt; 255

&lt;211&gt; 766

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (107)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (709)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (722)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (732)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 255

```

aaaggggggc gagtaactca agtgttagaa gttcgttgac ttttgactgg ggagaaagga 60
accttaaaact tggggaggag aaggaggatcc tggagttggt acctaanaac aaagatgggg 120
cggaatggag gctacagccc gaaagccagg ccagcagtggt cgttcttctg tgtccccaag 180
tagtggactt gagcccgtg agacctcggc aggagtctcg tcccaggga ggtgggtgtg 240
cggggtgagc cgcggagcgg ttccagctcg ggtaaagagg aagttacctc gggtcctttg 300
cactccaaact cggcggcgcc cgagcccagc gggccccagc caaccgcagc cccgtgtgtt 360
gtgtgtgtct aacacccggt ccgtgcgrgc gccgcgcgc ccgcgctgcc cccagctcga 420
ggaggacatc gcggccaagg agaagttgct gcgggtgtcg gaggacgagc gggaccgggt 480

```

## 162

```

gctggaggag ctgcacaagg cggaggacag cctcctggcc gccgaagagg ccgcgccaag 540
gctgaagccc gacgtagctt ctctgaacag acgcatccag ctgggttgagg aagagttgga 600
tcgtgcccag gagcgtcttg caacagcttt gcagaagctg gaggaagctg ataaggcagc 660
agatgagagt gagagaggca tgaaagtcac tgagagtcga gcccaaaang gatgaagaaa 720
anatggaaat ttaggagatc caactgaaag aggcaaagca cattgc 766

```

&lt;210&gt; 256

&lt;211&gt; 1394

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1238)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 256

```

gccacgcgt ccgagctcag tcagcagaag agataaaagc aaacaggctc gggaggcagt 60
tctgttgcca ctctctctcc tgtcaatgat ggatctcaga aataccccag ccaaattctc 120
ggacaagtcc attgaagact atctcttgcc agacacgtgt ttccgcatgc aaatcaacca 180
tgccattgac atcatctgtg gggttcctgaa ggaaagggtg ttccgaggta gctcctaccc 240
tgtgtgtgtg tccaagggtg taaagggtgg ctctcaggc aagggcacca cctcagagg 300
ccgatctgac gctgacctgg ttgtcttctc cagtcctctc accacttttc aggatcagtt 360
aaatcgccgg ggagagttca tccaggaaat taggagacag ctggaagcct gtcaaagaga 420
gagagcattt tccgtgaagt ttgagggtcca ggctccacgc tggggcaacc cccgtgcgtc 480
cagcttcgta ctgagttcgc tccagctcgg ggagggggtk gagttcgatg tgctgcctgc 540
ctttgatgcc ctggattttg cccgwacagg tcaattgact ggcggtata aacctaacc 600
ccaaattctat gtcaagctca tcgaggagtg caccgacctg cagaaagagg gcgagttctc 660
cacctgcttc acagaactac agagagactt cctgaagcag cgccccacca agctcaagag 720
cctcatccgc ctagtcaagc actggtacca aaattgtaag aagaagcttg ggaagctgcc 780
acctcagtat gccctggagc tcctgacggt ctatgcttgg gagcgaggga gcatgaaaac 840
acatttcaac acagcccagg gatttcggac ggtcttggaa ttagtcataa actaccagca 900
actctgcac tactggacaa agtattatga ctttaaaaac cccattattg aaaagtacct 960
gagaaggcag ctacagaaac ccaggcctgt gatcctggac ccggcggacc ctacaggaaa 1020
cttgggtggt ggagacccaa aggggttgag gcagctggca caagargctg aggcctggct 1080
gaattaccca tgctttaaga attgggatgg gtccccagt agctcctgga ttctgctggt 1140
gagacctcct gcttctctcc tgccattcat ccctgcccc ctccatgaag cttgagacat 1200
atagctggag accattcttt ccaaagaact tacctctntc gcaaaggcca tttatattca 1260
tatagtgaca ggctgtgctc catattttac agtcattttg gtcacaatcg agggtttctg 1320
gaattttcac atcccttgtc cagaattcat tcccctaaga gtaataataa ataattctca 1380
acacaaaaaa aaaa 1394

```

&lt;210&gt; 257

&lt;211&gt; 1329

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 257

```

ctcatcctca acctggtgac agacttgaag cccagatgc tgttggacac agtgccctgt 60
atccccgcct acatcctcta catgtgcac cggctcgcg accaaaccaa tgatgatctc 120
aagggtgcmct ccctgmtgac ctccaccayc aacggcatta agraagtcct gaaraagcac 180

```

163

```

artgatgact ttgagatgac gtcattctkg ttatccaaca cctgccacct tcttcaactgt 240
ctgaagcggg acagcgggga tgagggcttc atgactcaga atacwgcaaa gcacaacgaa 300
cactgyctta agaaytttga cctcaccgaa taccgtcagt actgagcgac ctttccattc 360
agatctacca gcagctcwtt aaaattgccg aggggyggtt acagccgatg atagtttctg 420
ccatgttggg aaatgagagc attcaggggtc tatctgggtg gaagcccacy ggctmccrga 480
agcrctcctc cagcatggca gatggggata actcatacyg cctggaagct wtcacccgcc 540
agatgaatgc ctttcatata gtcatgtgtg accagggctt ggaccctgag atcatcctgc 600
aggtattcaa acagctcttc tacatgatca acgcagtgc tcttaacaac ctgctcttgc 660
ggaaggacgt ctgctcttgg agcacaggca tgcaactcag gtacaatata agtcagcttg 720
aggagtggct tcggggaaga aaccttcacc agagtggagc agttcagacc atggaacctc 780
tgatccaagc agcccagctc ctgcaattaa agaagaaaac ccaggaggac gcagaggcta 840
tctgctccct gtgtacctcc ctacgacccc agcagattgt caaaatttta aacctttata 900
ctcccctgaa tgaatttgaa gaacgggtaa cagtggcctt tatacgaaca atccaggcac 960
aactacaaga gcggaatgac cctcagcaac tgctattaga tgccaagcac atgtttcctg 1020
ttttgtttcc atttaatcca tcttctctaa ccatggactc aatccacatc ccagcgtgtc 1080
tcaatctgga attcctcaat gaagtctgaa gatgcatgtt tccagcatta gtttgattcc 1140
caatgtgagc aagaaggaag tatatacagt aaagtaaatt caaggatctg ttaaactctg 1200
taaaagtaga tcaaatcaga gattgacagc ctgtggaggg tgctgaacta tacagaatta 1260
gacacaacta tgtcattatt tttgtacct actgctcaga ataaaaacac ttgaaatatg 1320
aaaaaaaaa 1329

```

&lt;210&gt; 258

&lt;211&gt; 2196

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 258

```

aattcggcag agcgggaagt cgctgaagac agagcgatgg tagttctgga ggcctcgctc 60
cggggccgac ccgaggccac agtgccctcg cggtagaccg gacttgggtg acgggctccg 120
ggctcccag gtgaagagca tcgggggctg agggatggaa gggcttaaga cgtccaacaa 180
cagcaccatg caggtgagct tcgtgtgccg gcgtgcagc cagccccga aactggacac 240
gagtttcaag atcctggacc gtgtcaccat ccaggaactc acagctccat tacttaccac 300
agcccaggcg aaaccaggag agaccaggga ggaagagact aactcaggag aggagccatt 360
tattgaaact cctcgccagg atgggtgtct tcgcagattc atccccccag ccaggatgat 420
gtccacagaa agtgccaaca gcttcaactc gattggggag gcatctgatg gcggcaccat 480
ggagaacctc agccgaagac tgaaggtaac tggggacctt tttgacatca tgctcggcca 540
gacagatgtg gatcaccac tctgtgagga atgcacagat actcttttag accagctgga 600
cactcagctc aacgtcactg aaaatgagtg tcagaactac aaacgctgtt tggagatctt 660
agagcaaatg aatgaggatg acagtgaaca gttacagatg gagctaaagg agctggcact 720
agaggaggag aggctgatcc aggagctgga agacgtggaa aagaaccgca agatagtggc 780
agaaaatctc gagaaggctc aggctgaggc tgagagactg gatcaggagg aagctcagta 840
tcagagagaa tacagtgaat ttaaaccgaca gcagctggag ctggatgatg agctgaagag 900
tgttgaaaac cagatgcgtt atgcccagac gcagctggat aagctgaaga aaaccaacgt 960
ctttaatgca accttcaca tctggcacag tggacagttt ggcacaatca ataacttcag 1020
gctgggtcgc ctgcccagtg ttcccgtgga atggaatgag attaatgctg cttggggcca 1080
gactgtgttg ctgctccatg ctctggccaa taagatgggt ctgaaatttc agagataaccg 1140
acttgttcct tacggaaacc attcatatct ggagtctctg acagacaaat ctaaggagct 1200
gccgttatac tgttctgggg ggttgcgggt tttctgggac aacaagtttg accatgcaat 1260
ggkggcttct ctggactgtg tgcagcagtt caaagaagag gttgagaaag gcgagacacg 1320
ttttgtctt ccctacagga tggatgtgga gaaaggcaag attgaagaca caggaggcag 1380
tggcggctcc tattccatca aaaccagtt taactctgag gagcagtgga caaaagctct 1440

```

164

```

caagttcatg ctgacgaatc ttaagtgggg tcttgcttgg gtgtcctcac aattttataa 1500
caaatgactt ttttccttag ggggagggtt gccttaaagg cttttaattt tgttttgttt 1560
gcaaacatgt tttaaattaa attcgggtaa tattaaacag tacatgttta caataccaaa 1620
aaagaaaaaa tccacaaaag ccactttatt ttaaaatata atgtgacaga tactttccag 1680
agctacaaca tgccatctat agttgccagc cctggtcagt tttgattcct aaccccatgg 1740
actcctttcc ctttcttctc tgaaaaaaac taattttaat ttgcttttct tttttttaac 1800
tgagtgaat tgagattgat gtgttttcac tggattttta tctctctcaa cttcctgcac 1860
ttaacaatat gaaatagaaa cttttgtcct tactgagatg aggatatgtt tgagatgcac 1920
agtgggataa tgtgggaaaa tgacatctaa gctttacctg gtcaccatgt gatgtgatca 1980
gatgcttgaa atttaacact tttcacttgg ttcttatact gaatgccgac tctgctctgt 2040
gtagagata tgaaatgggtg tttgatactg tttgagacat tatggagaga tttaattatt 2100
tgtaataaaa gatttgctgc agtctgaaaa ctgccagggt gtgcactgtt gggtttttct 2160
ttaaataaga gtactttgta ttctgggaaa aaaaaa 2196

```

&lt;210&gt; 259

&lt;211&gt; 567

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (236)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 259

```

gtttacataa gagatccttt agtccactca acggctgaca ttagcagcat ctttaataca 60
actgtttgtt caaaggcaag gtgggtccctt taaaggttac acttctagac tcacctgttc 120
tcactccctg ttttaatgta acccagccat gagatgccag ataatagaat tgctacctac 180
tagctgaaca ggaaagaacc tgtgctgttt ctgacacttc ttgttgcaaca tagatnaata 240
caatgggtat tatagagact cagttgcaga aattaacaaa catgctgctt gggttaaatg 300
ggtagactca tctggctcat tctttattcc atttttagttg gtttgcactt tgcctaaggt 360
gcatactcca aactyttggt attattctcc tgatagtcac actagtagtc tccctgggtg 420
gctataatct ctaaaagctt taaatgtttg cwtgcagcta tccatcgaat gtcaaagtgt 480
ctctcttttg ctggaatgac aaaactcaaa ggaatgtgtg atcaggaaga catcataacc 540
tatgaatgat ggaacccaaa atgaatg 567

```

&lt;210&gt; 260

&lt;211&gt; 950

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 260

```

gactaatgaa ataactgttc actattgtgg gttctacttg cagggttcag actaggcaat 60
gtggtagatg ctatacaggc aactgagcag agcattcatg ccactgacct ggtacctgcg 120
ttatgcttaa cattagccaa cctgaaccgt gtgatttatt tcatctgtga caccatcttc 180
tgggtgagga gcgtaggtct cacctctggc atcaacaaa agaaatggcg aacgagggtc 240
gctcaccact actactattc tcttctgctg agccttgctc gggatctgta tgaaatctcc 300
ctgcagatga aacgagttac atgtgacagg gcaaagaaa agaaatcagc atcccaggat 360
cctcttttgt tcagcgtggc tgaggaggwa acagaatggc tccaatcctt tctacttctt 420
ttattccgat ctctgaagca gcatectccc ttgctcctgg acacagtga gaacctttgt 480
gatatactga acccttttga cctgctgggg atctataaat ccaatcctgg catcattgga 540

```

## 165

```

cttgagggtc ttgtgtcctc tatagcaggc atgatcactg tggcatatcc tcagatgaag 600
ctgaagaccc gttagtgttt ttaggcttgg aactagtacc tactttaaaa gatggcctct 660
tggtgggaca gacatttgta taagtcacag gccatgtcat actgtgctta agttcttggt 720
catgtgagca tttacaacac tgtgatgtgg gcagagatga ggccaagaac ggagaaggga 780
ggagcatgaa gagttgtatg tttttggagt gctggagtga cttgtgaatt tctgaatatt 840
ttcccttcat ctaacattga ttgaacatct cttatgtgca tagtgggagc ttagtatttg 900
ctgaatgaat aaaaattgaa aggaaaaaat ttaaaaaaraa aaaaaaaaaa 950

```

&lt;210&gt; 261

&lt;211&gt; 475

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (444)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (451)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (454)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (470)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 261

```

caaagaattc ggcacgaggt ctgatcttcc tgcggctgaa ccgcccggct gagccgacat 60
tgccggcgct ttggcgattc ggcccgaacga gctccgcttt cgctacagca tgggtggccta 120
ctggagacag gctggactca gctacatccg atactcccag atctgtgcaa aagcagtgaag 180
agatgcactg aagacagaat tcaaagcaaa tgctgagaag acttctggca gcaacgtaaa 240
aattgtgaaa gtaaagaagg aataatctac cctgactaaa gcttgaaatg ctacatttcc 300
aagggtgaaga tgtgtgggca catgttatgg cagattgaaa aggatctcat tccatgggaa 360
aaaaaaaaat cctgtcttgt tcataaattg acaatgtcaa taaattgaaa tatggttcac 420
tgttaaaaaa aaaaaaaaaa aaangggggg nccnttttaa agaattccaan tttac 475

```

&lt;210&gt; 262

&lt;211&gt; 1244

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1230)

166

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1232)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1235)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 262

```

ggcacgagga aagtactttt gctataagtt tcctaaaagt atttaatact tttttttttc 60
aatttagatt aaatctcttg atgaacagtg tgtggttggc aaaatttcca agcactggac 120
tggaattttg agagaggcat ttacagacgc tgataacttt ggaatccagt tccctttaga 180
ccttgatggt aaaatgaaaag ctgtaatgat tggtgccgtt ttcctcattg acttcatggt 240
ttttgaaaagc actggcagcc aggaacaaaa atcaggagtg tggtagtgga ttagtgaaaag 300
tctcctcagg aaatctgaag tctgtatatt gattgagact atctaaactc atacctgtat 360
gaattaagct gtaaggcctg tagctctggt tgtatacttt tgcttttcaa attatagttt 420
atcttctgta taactgattt ataaagggtt ttgtacattt ttttaatactc attgtcaatt 480
tgagaaaaaag gacatatgag tttttgcatt tattaatgaa acttcctttg aaaaactgct 540
ttgaattatg atctctgatt cattgtccat tttactacca aatattaact aaggccttat 600
taatttttat ataaattata tcttgtccta ttaaacttag ttacaattta tttcatgcat 660
aagagctaag gttatttttg aaatgccata tattcaaaaa agctcaaaga taattttctt 720
tactattatg ttcaaataat attcaatatg catattatct ttaaaaagtt aaatgttttt 780
ttaatcttca agaaatcatg ctacacttaa cttctcctag aagctaactc ataccataat 840
attttcatat tcacaagata ttaaattacc aatttttcaa ttattgttag taaagaacaa 900
aatgattctc tcccaaagaa agacacattt taaatactcc ttcactctaa aactctggta 960
ttataacttt tgaaaagttaa tatttctaca tgaaatgttt agctcttaca ctctatcctt 1020
cctagaaaat ggtaattgag attactcaga tattaattaa atacaatatc atatatatat 1080
tcacagagta taaacctaaa taatgatcta ttagattcaa atatttgaaa taaaaacttg 1140
atttttttgt aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1200
aaaaaaaaaa aaaaaaaaaa gggcgggccgn tntanaggat ccaa 1244

```

&lt;210&gt; 263

&lt;211&gt; 1132

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 263

```

cttccaactt ggtacctgtg gatatcatag aaagtgtagt ttcaaaggag atggacaaac 60
gatacttaca gtttgatatt aaggcctttg ttgaaaataa tcttgccatt aaatgggtgc 120
ctactccagg ctgtgacaga gcagtaagac taacgaaaca aggggtcaaat acatctggat 180
ctgatacact cagcttccca ttgctgagag ctctctgctg tgattgtgga aaaggacacc 240
tcttctgctg ggagtgcctt ggtgaagcac atgagccttg tgactgcca acatggaaga 300
attggctgca aaaaataacc gaaatgaaac cagaagaact tgtgggagtt agtgaagcct 360
acgaggatgc cgccaattgt ctctgggtat taactaactc caagccttgt gccaaactgta 420
agtctccaat acagaagaat gaaggctgca atcacatgca gtgtgctaag tgcaagtatg 480
acttttgctg gatttgctt gaagagtgga aaaaacatag ttcgtccact ggaggttatt 540
acagatgtac tcgctatgaa gtcattcaac acgtggagga gcaatccaag gaaatgactg 600

```

167

```

tggaggctga gaaaaaacac aaacgatttc aggaacttga cagatttatg cactattata 660
caagatttaa aaaccatgag catagtattc agctagaaca acgccttctt aaaacagcca 720
aagaaaagat ggagcaattg agcagagctc tcaaagaaac tgaaggaggc tgtccagata 780
ccactttcat tgaagatgca gttcatgtgc tcttaaaaac tcggcgcatt ctcaagtgtt 840
cttatccata tggatttttc ttggaaccta aaagcacaaa gaaagaaatt tttgaactaa 900
tgcaaacaga cctagaaatg gtcactgaag accttgccca gaaagtcaat aggccttacc 960
ttcgcacacc ccgccacaag atcatcaaag cagcatgcct tgtacagcag aagaggcaag 1020
aattcctggg catctgtggg ctcgggggag tagctcctgc agactcacca gaagcttcca 1080
aggcgcattt tgstggtggg aacatggggr ttgggggrata tttwgggggtt tt 1132

```

&lt;210&gt; 264

&lt;211&gt; 499

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (447)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (466)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (467)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (469)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 264

```

ggcacgagtg aagctgaagt actgcttcac ctgcaagatg ttccggccac cccgaacctc 60
aactgacagt gtctgcgaca actgtgtgga acgatttgac catcactgcc cctgggtggg 120
caactgtgtg gggagacgga actatcgctt cttctacgcg tttattctct cctctcatt 180
cctgacggcc ttcattcttcg cctgtgtggt caccacactg acgttgcgcg ctgagggaag 240
caacttcctc tccactctga aggagacacc agcaagcgtg ctgggagttg gtgatctgct 300
tcttctccat ctggtccatt ctgggcctct cagggtttca cacgtacctc gtegcctcca 360
acctgactac taatgaagac atcaaagggt cggttggtcca gcaagagggc ggtgagcctc 420
ttgtcaaccc tacagcataa agtatnttca ccaatggcgg gtgggnntng ggccttaact 480
tccagctatt gacggggggg 499

```

&lt;210&gt; 265

&lt;211&gt; 735

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

168

<220>  
 <221> misc feature  
 <222> (648)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (713)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (730)  
 <223> n equals a,t,g, or c

<400> 265  
 ggagacacca ccattcctct cagcctgtgt ctgtctcaaa ggccccacct cacctcccct 60  
 aaaggcagcc gctgcagtcg ccacacctt gccctgtctg cgatgacctt gtcgccactt 120  
 ctgctgttcc tgccaccgct gctgctgctg ctggacgtcc ccacggcggc ggtgcaggcg 180  
 tccccctctgc aagcgttaga cttctttggg aatggggccac cagttaacta caagacaggc 240  
 aatctataacc tgccggggggc cctgaagaag tccaatgcac cgcttgtcaa tgtgaccctc 300  
 tactatgaag cactgtgctg tggtgcccga gccttcctga tccgggagct cttcccaaca 360  
 tggctgtttg tcatggagat cctcaatgtc acgctgggtg cctacggaaa cscacaggaa 420  
 caaawtktca ktggcagggtg ggagttcaag tgccagcatg gagaagagga gtgcaaattc 480  
 aacaagggtg aggccctgct gttggatgaa cttgacatgg agctagcctt cctgaccatt 540  
 gtctgcatgg aagagtttga ggacatggag agaagtctgc cactatgctg cagctctacg 600  
 cccaggctgt cgcagaacta tcatgagtgt gcaatgggac gcggcatnag tcatcacgca 660  
 acgccacgac agatctctca gcacaaagat atgtcctggt acgcaatgga acntgagata 720  
 accagtctan ctgtt 735

<210> 266  
 <211> 851  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc feature  
 <222> (834)  
 <223> n equals a,t,g, or c

<400> 266  
 ctattggtgt gaacagtgtg atgtacaatt ctccctcaagc agtgaactct acctacattt 60  
 ccaggagcac agctgtgatg aacagtactt gtgtcagttc tgtgaacatg aaactaatga 120  
 tccagaagac ttgcatagcc atgtggtaaa tgagcatgca tgtaaattaa tagagttaag 180  
 tgataagtat aacaatggtg aacatggaca gtatagcctc ttaagcaaaa ttacctttga 240  
 caaatgtaaa aacttctttg tatgtcaagt atgtggtttt cggagtagac ttcacacaaa 300  
 tgtaaacagg catgttgcta ttgaacatac aaaaattttt cctcatgttt gtgatgactg 360  
 tgggaaaggc ttttcaagta tgctagaata ttgcaagcat ttaaattcac atttatctga 420  
 agggatttat ttatgtcaat attgtgaata ttcaacaggga caaattgaag atcttaaaat 480  
 tcatctagat ttcaagcatt cagctgactt gcctcataaa tgtagtgact gcttgatgag 540  
 gtttggaat gaaagggaat taataagtca ccttcacgtc catgagacaa cttgattatt 600



169

```

ctctttaact tacagaatgt tagtttaaaa taataaatcc atcctttttt tggagatgat 660
taaattggatg attgtaaaaca caacttatga aatctgcctt taacaagtaa ctttttttaa 720
ttataaaatt ttattggcat tgctccattt tctgtatata aatatacttt taatgtggta 780
ttttcaaaaa aaaaaaaaaa aaaaaaatcc acgcggccgc gaattcccgg gtcnaacaag 840
ctcactaatc c 851

```

```

<210> 267
<211> 1257
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (51)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (118)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (1213)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (1217)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (1238)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (1245)
<223> n equals a,t,g, or c

```

```

<400> 267
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tcaaattcga acaggccaaa gtttcagcct gtatattgcg cgcaatcatc agcggacncg 120
gtgatgaagt gatcgaaactg gcgaaaacaa atgggctaagg taaaaagggt ggcatttccg 180
tcataataag gacatgccat gattgattta cgcagtgata ccgttaccgg accaagccgc 240
gccatgctcg aagcgatgat ggccgccccg gttggggacg acgtttacgg agacgaccct 300
accgttaatg ctctgcagga ctacgcagca gagctttccg gtaaagaagc cgccattttt 360
ctgcctaccg gcaactcaggc caacctggtc gctctgctca gtcactgcga acgcggcgaa 420
gagtatattg tcggtcaggc cgcgcataac tatctgtttg aagccggtgg cgcggcggtg 480
ctgggcagta ttcaaccgca acccatagac gcggctgccg acggcacgct accgctggat 540

```

170

```

aaagtggcga tgaaaatcaa acccgacgat atccatttcg cccgcaccaa attactcagt 600
ctggaaaaaca cccacaacgg caaagtgttg ccgcgggaat acctgaaaga agcatgggaa 660
tttaccgcgcg agcgcaatct ggcgctgcat gttgacgggtg cgcgcattctt taatgccgtg 720
gtggcttacg gctgcgaact gaaagagatc acgcaatatt gtgattcggt caccatttgc 780
ctgtcgaaaag gtcttgggac gccagtcggt tcattactcg tcggtaatcg tgattacatt 840
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gctgccgccg ggatatatgc cctgaaaaat aacgttgccg gcttgcagga agaccacgac 960
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ccaatatgct gtttgttcgc gtcggggaag aaaatgctgc cgcgttaggc gaatacatga 1080
aagcgagaaa cgtgctgatt aacgcctcgc cgattgtccg cctgggtgacg catcttgacg 1140
tctcgcgcga acaactggcg gaagtcgccg cccactggcg tgcattcctg gcgcgttaag 1200
gagagaaacg ttncgcnaag cattttagtt ctccgtgnca attgntacat tgtcaac 1257

```

&lt;210&gt; 268

&lt;211&gt; 1085

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1067)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1081)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1083)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 268

```

gcaaaatttt agcatctctc aataatcata ctttttctct ttaattatca acaaaatatt 60
ttcatgttaa gctatctctt gcattcctag aataactcta cttgatcatg atgttttttc 120
ttttaataat ggaattataa ataagtatac agtttttgta tgaaaatgtt tttatttctc 180
tggagcatgt acctatggat ggaattacta aatcatatgc tagttctgtg ttttaactatt 240
tgaaggattg aaggagtgcc agattgtttt ccaaagtggc tgtaccattt tacattccta 300
cctgcagtgt atgaaggttt caatttctcc acatcctcac caatattatt atctgtcttt 360
ctgattgtag ccatcctagt ggggtgtgaag tggatatctt gtgacttgga tttgattttc 420
cctgatggct aatgatattg aacatctatc tttctctgtg cttattgggtc atttgatatat 480
tttcttttga gaaatgtcta ttccagatcc yttttctgtt tttaaaaaat arctttattg 540
aggtwtatth gacaaataaa aatttgktgt atatttataa tgtatttata agaaaattga 600
gagaaaggac tacagagccc cgaattaata ccaatagaag ggcaatgctt ttagattataa 660
atgaagggtg cttaaacagc ttaaagttta gtttaaaagt ttaggtgatg taaaataatt 720
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gacgcaggga gaattgcgtc atttaaagcc tagttaacgc atttactaaa cgcagacgaa 840
aatggaaaaga ttaattggga gtggttaggat gaaacaattt ggagaagata gaagtgttgaa 900
gtggaaaact ggaagacaga agtacgggaa ggcgaagaaa agaatagaga agatagggaa 960
attagaagat aaaaacatac ttttagaaga aaaaagataa atttaaacct gaaaagtagg 1020

```

171

aagcaraara aaaaaaaaaa aaaaaaaaaa aaaaaagggc ggccgcncctg gggccccagc 1080  
ntncg 1085

&lt;210&gt; 269

&lt;211&gt; 1315

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 269

ggcggcagcg ccggaaaagga ggccaagagc gcgggcgggcg aggcaagatg ggggcaacca 60  
agaggaaaacg gcgtggaggc tttgcagttc aggccaagaa gccaaaaaga aacgaaatag 120  
atgcggagcc gccagctaag cggcacgcca cagcagagga ggtggaggaa gaagagaggg 180  
accggatccc aggccccgtt tgcaagggaa agtggaaaaa taaggaaacgg attctcatct 240  
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tgcctcattc taaagcagat actaaaatgg atcgtaaagga taagctatct gtgattaacg 360  
aggttttgtga aatgaagaac tgtaataaat gcattctatct tgaagctaag aaaaaacagg 420  
atctctatat gtggctttca aattcacctc acggaccatc tgctaaattc cttgttcaaa 480  
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tgtttacttt caccattttg gataatagga tatggtttcg gaactttcag atcatagaag 720  
aagatgctgc tcttgtagaa ataggacctc gttttgtctt aaatctcata aagattttcc 780  
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caaaagttga tttgaaagca agaaagaaac ggatttacia aaggcaaaga aaaatgaaac 1080  
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tttctaaata aaatatcacc agaattcatc agttaaaaaa aaaaaaaaaa aaaaa 1315

&lt;210&gt; 270

&lt;211&gt; 2959

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2948)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2956)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 270

ccattcccgg gtcgaccac gcgtccgctg gaaatttggg ttctccagaa ggtggtttcg 60  
atgccatcat gcaagttgca gtttgtggat cactgattgg ctggaggaaat gttacacggc 120  
tgctggtgtt ttccacagat gccgggtttc actttgctgg agatgggaaa cttggtggca 180

172

```

ttgttttacc aaatgatgga caatgtcacc tggaaaataa tatgtacaca atgagccatt 240
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caatttttgc agttactgaa gaatttcagc ctgtttacaa ggagctgaaa aacttgatcc 360
ctaagtcagc agtaggaaca ttatctgcma attctagcaa tgtaattcag ttgatcattg 420
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tcttgactct gatgtatttt awcaggttgt gtgcatgaaa tttttataga taaagragtt 2940
gaggaaanaa aaaaanaaa 2959

```

&lt;210&gt; 271

&lt;211&gt; 2025

&lt;212&gt; DNA

173

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1339)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1916)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1944)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 271

```

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tctgactttt aataatggta ataggaaaac aaaacccaaa gcttttcaga acttcagtgt 120
gaggtttcct attttracaa gttaacttgt aaatactcag gttttacgat gtataattta 180
cctaatagac caaactaact catggagata ttttgaacta ttatttaggt acaaacttta 240
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tgaacatatt taaaatacat tttcacagaa tggatgaatt agttgtttct tcagagttac 360
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agtttttaaac caccaaacca atatttttcc tttaaatttt aatcttataa tatagaaatc 600
ttatgtaaat gaaattttgt catgtttcaa ataaagagaa ctgaagtaga aaatagaaat 660
gccagtaaac aacataatgt ttaatttaca acttacatta ggggtttggg ggaatgctaa 720
ttatatattg agaataataca ttagaactct tcaaaatggg ctcttctaata gaggtcacta 780
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gaagtgatcc ctggtcatcc taataatggg atgaggggag tttccagcag atttcagggt 1020
gttcttaaaag tttttgttgg tcattttctc aatagtacat gaaatcaaga tgcttatgag 1080
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actgttacgt aatgcagttt gatgttgtaa cctaacattc caaaaaaaaa attganaggg 1920
ggaatctcaa aatagtatat actncactaa cttgtttaca ggtgctgtat ttaaaagcat 1980

```

174

gcttctctct caaaaagaaa aattaaagga ttttattgcc aaacc

2025

&lt;210&gt; 272

&lt;211&gt; 852

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (767)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (769)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 272

```
ccaccgcgcca caaggcccag ctaatTTTTg tatttttagt agagacaggg tttgattatg 60
ttggacaggc tgggtctcaaa ctctgactt caagtgatcc acccgccctcg gcctcccaac 120
gtgawgggac tatagacatg agccatcgtg cytggccttc ttgawtcttg aatacgggggt 180
tttgagggtga aagcatttca tgaaaactta agttcataca caagagcatc atgaatattc 240
taaaagaggt atctgtgctt tttttgtgac cacaaaatat tacttcttat gaaatgttta 300
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aaatgacttc aagttttcaa ttttttaaaa taacttaaaa atcttagcaa gggggaaact 840
tttttttaag gg 852
```

&lt;210&gt; 273

&lt;211&gt; 571

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (7)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (535)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 273

gcccaantac tttccagccc agtaaggggt atttcaggag agcagtcac tkaaggttct 60

## 175

```

ttccctttaa gatatgtgca ggatcaagtt gcggcacctt ttcagctgag taaccacact 120
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tgtcagaaca gctgtgagaa ggggaacacc accactctca ttagtgagaa tggtcâtgtct 240
gccgacaccc tgacggccac gaacttccga gtggtaatth gccatcttcc atgtatgaat 300
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ggcaaggcat tggggacgca tgtcatccat tcaacacata ccttgccctc gaccgtgact 480
agccagcagg agtcaaagtg aaatttcttc cttaacatag tcaatatcca tgtgnaacat 540
cctcctgaag cttccgtcca gatacatcag g                                     571

```

&lt;210&gt; 274

&lt;211&gt; 710

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (667)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (689)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (701)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 274

```

gtaagtttga gagcatctgc tggaaaacca ctagaatttg caaacggcca cctcaaaata 60
ctccagccag tcccactaag ccaaagacca gaatctgaga acagggatgg ggaaattatt 120
cctttctgtg gatgattatg cagctgggcc atgatttcac acccgggggc catgggctaa 180
gatggagggg aaggaaggaa tgtaatgtgt gccctctacc tcttcaccag gcatcatcct 240
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ggaccttgct ttgggacctt acacacttcg gctctctgga cacttgcgac acytcaaggt 480
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```

&lt;210&gt; 275

&lt;211&gt; 595

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 275

```

taaaagagtg tcctaacagt ccccgggcta gagaggacta aggaaaacag agagagtgtt 60

```

## 176

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ggtgggctcc tggggcgccct gcgcagatgg gccacagaag ggcaggccgg agctgcacac 360  
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cctgggtttt cccaccgga gatgaaggat acgctgtatt tttgcctaa tgtccctgcc 480  
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<210> 276

<211> 1172

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (119)

<223> n equals a,t,g, or c

<400> 276

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ttctgaagct gcttcctctt ataaaatagc ttttgccgaa acatagtttt tttttagcag 180  
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<210> 277

<211> 780

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (161)

<223> n equals a,t,g, or c



177

<220>  
<221> misc feature  
<222> (773)  
<223> n equals a,t,g, or c

<400> 277  
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<210> 278  
<211> 2375  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (9)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (920)  
<223> n equals a,t,g, or c

<400> 278  
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cccagtcagt taatggatca cccaagcgg aacaaccttc attggaatct acaagcaaag 240  
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gtttctggcc agacagccca tcccagacc gatttgggat gttgccctg gatgagcctg 540  
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tcaaattagg ctcagacatc caagtccacg tcaactgcctg tattctctct gtgtgtggct 780  
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## 178

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&lt;210&gt; 279

&lt;211&gt; 2461

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (14)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1164)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 279

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tttcaattct tggnttttctg ttcccttcta ccaaaaccca gcataggact cagtgtacac 60
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cttgagtata caagttccac actcattacc tttcagtggt gacccatcac ccactacaat 420
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179

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ctctgtatatt ggacctgcag atgtttgtgta cagaaccgat gcatggcagg gtcaggaagc 540
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t 2461

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&lt;210&gt; 280

&lt;211&gt; 2520

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 280

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accacttgca ctccagcctt gaacagagtt aggatcctgt caaaaaagaa aagaaaaaga 60
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aaaaagaaga cgctgttcca tcgccttttt ataagtcctt ctctccacac ctaaaagcag 180
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acaagccatg tagcctctct gtgcctatct cttcatgcat aaactgggac tcataatatt 540
tgtaaaatgt attgatactc tcagggcaaa ttcactatat tgctatacag ttgagatcag 600

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180

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tggtgtaaaa ttaaactgat ctggttctaa ttgcctcaaa ggccaaagcc caggcatttg 660
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&lt;210&gt; 281

&lt;211&gt; 1448

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1427)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1432)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1440)

181

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 281

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ccaagttccg gccagttcga cctcgaggat ccagaggtgg agacggtact acctcccagc 120
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cgtgatccctt yatgcccggc ccctgcccct ccctccgggt ggaacttccc cctcacccgc 240
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caaggga 1448
```

&lt;210&gt; 282

&lt;211&gt; 827

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (725)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (800)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (814)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

182

&lt;222&gt; (815)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (817)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (819)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 282

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gtcctgtagt tgtcccccct ggaaaggaga aggaggcaga aagaagatgg aaagaaggaa 120
acttcaatgt ctaccttagc gatttgatcc cagtggatag agccattgaa gacaccagac 180
ctgctggatg tgcagagcag ctagtgcaca ataacctccc aaccaccagt gtcatcatgt 240
gctttgtgga tgaagtgtgg tccactctcc tgagatctgt tcacagtgtc atcaatcgct 300
ctcctccaca cctcatcaag gagattctgc tggtagatga cttcagcacc aaagactatc 360
taaaagataa tttggataaa tacatgtccc agtttccaaa agttcggatt cttcgccctca 420
aagagagaca tggcttaata agggccaggc tggcaggagc acagaatgca acaggtgatg 480
tggtgacatt tttagattct catgtggaat gtaacgttgg ttggttgga cctcttctgg 540
aaagagttta ttttaagtaga aagaaagtgg cctgtccagt aatcgaagtc atcaatgata 600
aggatatgag ttacatgaca gtggataact ttcaaagagg catctttgtg tggcccatga 660
actttggttg gagaacaatt cctccagatg tcattgcaaa aaacagaatt aaagaaactg 720
atacnataag gtgccctgtc atggctgggtg ggattggttt ctattgccaa aagttacttt 780
ttttgaactt ggaacatacn aacccttggc cttnnangnt ttggggg 827

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&lt;210&gt; 283

&lt;211&gt; 524

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (518)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (524)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 283

```

gcgcatttgg cgcctccct accgetccaa gccagccct cagccatggc atgccccctg 60
gatcaggcca ttggcctcct cgtggccatc ttccacaagt actccggcag ggagggtgac 120
aagcacaccc tgagcaagaa ggagctgaag gagctgatcc agaaggagct caccatkggc 180
tcgaagctgc aggatgctga aattgcaagg ctgatggaag acttggaaccg gaacaaggac 240
caggaggtga acttccagga gtatgtcacc ttcttggggg ccttggcttt gatctacaat 300
gaagccctca agggctgaaa ataaataggg aagatggaga caccctctgg gggtcctctc 360

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183

tgagtcaaat ccagtgggtgg gtaattgtac aataaatttt ttttgggtcaa atttaaaaaa 420  
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 480  
aaaaaacaaa aaaaaaaaaa aaaaaaaaaa aaaaaaanac aaan 524

&lt;210&gt; 284

&lt;211&gt; 613

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 284

cctcactaaa gggaacaaaa gctggagctc caccgcggtg gcggccgctc tagaactagt 60  
ggatcccccg ggctgcagga attcggcacg agccgcaggc cacgagaagc tgccggtgca 120  
cgtagaagac gccctcacct atctggacca ggtgaagatc cgctttggca gcgaccctgc 180  
cacctacaac ggcttcctgg agatcatgaa ggagtcaaaa agccagagca tcgatactcc 240  
tggagtcatc agacgtgtct cgcagctctt ccacgagcac cctgacctca ttgttggatt 300  
caacgctttt cttccccctc gatatagaat agacattccc aagaatggca agttaaacat 360  
acagtcgcct ctgacaagcc aggagaattc gcacaaccac ggggacggtg cagaggactt 420  
caagcagcag gtgccgtwta aagaggacaa accccagggtg cccctggagt ccgattccgt 480  
ggaattcaac aacgccatca gctatgtgaa taagattaaa acccgcttct agaccacca 540  
gaaattacag gtcattcctg gagatctgca cacstwccar aargarcarc tgaacacgag 600  
gggccggcca ttc 613

&lt;210&gt; 285

&lt;211&gt; 533

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 285

ggcacgagsg gcgggaacac gcggggccca agatggcggc cagccggtac cggcgttttc 60  
ttaagctctg tgaggaatgg ccagtggacg agaccaaacy gggccgggac ttgggcgctt 120  
acctgcgaca gcgggtagca caggcctttc gggagggaga gaataccag gttgcagagc 180  
ctgaggcctg tgatcagatg tacgagagct tagcgcgact ccattcaaac tactacaaac 240  
acaagtaccc tcgccccaga gacaccagct tcagtggcct gtcgttgga gagtacaagc 300  
tgatcctgtc cacagacacc ttggaagagc ttaaggaaat agataaaggc atgtggaaga 360  
aactgcagga gaagtttgcc cccaagggtc ctgaggagga tcataaggcc tgagctcagg 420  
ccttacctcg tgcacatacc taggtgtgga gtcttgtaca ttgccatcgt caataaaact 480  
gccccagttt ccccttgaaa aaaaaaaaaa aaaraaaaaa gaaaaaagtc gac 533

&lt;210&gt; 286

&lt;211&gt; 2071

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (303)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 286

caagcggaaa ataatgatca agcggcacga ggtggagcag cagaacattc gggaggaact 60  
aaataaaaaa aggaccaga aggagatgga gcatgccatg ctaatccggc acgacgagtc 120

184

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cmcccagagag ctagagtaca ggcagctgca cacgttacag aagctacgca tggatctgat 180
ccgttttacag caccagacgg aactggaaaa ccagctggag tacaataaga ggcgagaaaag 240
agaactgcac agaaagcatg tcatggaaact tcggcaacag ccaaaaaaact taaaggccat 300
ggnaatgcaa attaaaaaac agtttcagga cacttgcaaa gtacagacca aacagtataa 360
agcactcaag aatcaccagt tggaagttac tccaaagaat gagcacaaaa caatcttaaa 420
gacactgaaa gatgagcaga caagaaaact tgccattttg gcagagcagt atgaacagag 480
tataaatgaa atgatggcct ctcaagcggt acggctagat gaggctcaag aagcagaatg 540
ccaggccttg aggctacagc tccagcagga aatggagctg ctcaacgcct accagagcaa 600
aatcaagatg caaacagagg cacaacatga acgtgagctc cagaagctag agcagagagt 660
gtctctgctc agagcacacc ttgagcagaa gattgaagag gagctggctg cccttcagaa 720
ggaacgcagc gagagaataa agaacctatt ggaaaggcaa gagcgagaga ttgaaacttt 780
tgacatggag agcctcagaa tgggatttgg gaatttgggt acattagatt ttcctaagga 840
ggactacaga tgagattaaa ttttttgcca ttacaaaaaa aaaaaaaaaa aaagaaaaca 900
raaaaaaatt cagacctgct aaaaccacat tccccatttt aacgggcgct gctctcactc 960
tctctctctc ttactcttac tgacatcggt tcggactagt gcctgtttat tcttactcca 1020
tcaggggccc ccttctctcc cccgtgtcaa ctttcagtgc tggccaaaac ctggccgctc 1080
cttctattca cagtacacgt cacagtattg atgtgattca aaatgtttca gtgaaaactt 1140
tggagacagt tttaacaaaa ccaataaacc aacaacaaaa aaagtggatg tatattgctt 1200
taagcaatca ctcatcacca ccaatctgtg aaagtaaagc aaaaaataat aataataaat 1260
gccaaggggg agagagacac aatatccgca gccttacacc ttaactagct gctgcattat 1320
tttattttat tttatttttt tggattttat tcatcaggaa taaaaaaaac aaagttttat 1380
taaagattga aaatttgata cattttacag aaactaattg tgatgtacat atcagtgggtg 1440
acatattatt acttttttgg ggacgggggg tgggtggggg gaagagatct tgtgattttt 1500
aagaacctgc tggcaagagt ttaacttgtc ttcagcatat tctgattgta tcataatcat 1560
tttctgctgt tgcagaggat gtgaatacac ttaaggagct cacagaatcc cagtagcaca 1620
aattgggctt tggcaaatcg tgtattttgt gtatagaagg aatttaagga gaggtattac 1680
ttattttcat attgtatttt aactgtttct ctgatcaaat ttttttactt cctctctctg 1740
ttctcccca cctccctcct tttccagttc agtatttggg gttcaacact gtctctcaat 1800
cagatcatct tgatcttttt ctttatctcc cttcccttc ctaagtccca tttcttggtc 1860
ataaatattg cattattcac actttcaaac tgtgtatttt cttacaataa aaaatgatga 1920
aaaaaaaaaa ggctttactt cttttgcatg cactttaaaa acaaaaacaa acatttttca 1980
ggttccaagg aaragcatga taactgtcag agcttttaat tatatttgta aataaaagtg 2040
ttcatcacaa aaaaaaaaaa aaaaaaaaaa a
2071

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&lt;210&gt; 287

&lt;211&gt; 1966

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (56)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (788)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature



185

&lt;222&gt; (1753)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 287

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gaactagtct cgagtttttt ctgtctagct ccgaccggct gaggcggcgc ggcagnngag 60
ggacggcagt ctgcrcggc tactgcagca ctggggtgtc agttgttggc cgcaccaga 120
acgcttcagt tctgctctgc aaggatatat aataactgat tgggtgtgcc gtttaataaa 180
agaatatgga aactgaacag ccagaagaaa ccttccttaa cactgaaacc aatggtgaat 240
ttggtaaacg ccctgcagaa gatatggaag aggaacaagc atttaaaaga tctagaaaca 300
ctgatgagat gggtgaatta cgcattctgc ttcagagcaa gaatgctggg gcagtgattg 360
gaaaaggagg caagaatatt aaggctctcc gtacagacta caatgccagt gtttcagtcc 420
cagacagcag tggcccccag cgcataattga gtatcagtgc tgatattgaa acaattggag 480
aaattctgaa gaaaatcatc cctaccttgg aagagggcct gcagttgcca tcacccactg 540
caaccagcca gctcccgcct gaatctgatg ctgtggaatg cttaaattac caacactata 600
aaggaagtga ctttgactgc gagttgaggc tgttgattca tcagagtcta gcaggaggaa 660
ttattggggt caaagggtgct aaaatcaaag aacttcgaga gaacactcaa accaccatca 720
agcttttcca ggaatgctgt cctcattcca ctgacagagt tgttcttatt ggaggaaaac 780
ccgatagngt tgtagagtgc ataaagatca tccttgatct tatactctgag tctcccatca 840
aaggacgtgc acagccttat gatcccaatt ttacgatga aacctatgat tatggtggtt 900
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tggtcttatga accacagggt ggctccggat atgattattc ctatgcaggg ggtcgtggct 1320
catatggtga tcttggtgga cctattatta ctacacaagt aactattccc aaagatttgg 1380
ctggatctat tattggcaaa ggtggtcagc ggattaaaca aatccgtcat gagtccggag 1440
cttcgatcaa aattgatgag cctttagaag gatccgaaga tcggatcatt accattacag 1500
gaacacagga ccagatacag aatgcacagt atttgctgca gaacagtgta agcagtwma 1560
gwttagcttt gtgttagctt atacatacta aaaccttta aaagcttttc ttctcaattg 1620
atTTTTTct tttagaagcc atggtgtctc aaccttttgg ggacctaaact tctaaacatt 1680
ctaatagttt gccttaattt ttcttctgct ttcttactaa aaacgargac attcaatact 1740
aatcttgcc tgnaggaagc cttgaaccaa gcaaacttct gcatttctct ggtgaaaact 1800
gctgccaaaa ccacttgta aaaattgtac agagcctgta ggaaaatata gaaggttcca 1860
ttgggatgtt ggcctagttc tgtgtgggaa gacttagtgg attttgtttg tttttagata 1920
actaaatcgg ccaacaaatc accgttctgg cctatgggac cgggcc 1966

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&lt;210&gt; 288

&lt;211&gt; 869

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (869)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 288

```

gctctggcgg gcataccagc gggccctggc cgctcaccg tggaaagtac aggyctgac 60
agctgggccc tgtggttagga ggctggtaca aggttttggg tcggttcac cctggcacca 120

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## 186

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ccaaagtgga tgcactgaag aagatgttgt tggatcaggg gggctttgcc ccgtgttttc 180
taggctgctt tctcccactg gtaggggcac ttaatggact gtcagcccag gacaactggc 240
caaactacag cgggattatc ctgatgccct taccaccaac tactatctat ggcctgctgt 300
gcakttagcc aacttctacc tgggtccccct tcattacagg ttggccgttg tccaatgtgt 360
tgctgttatac tgggaactcct acctgtcctg gaaggccatc cggctctaag cctgcctcac 420
tccatcgttt ccaccttgca gtgatgcagc ttgacctggg aacggtcaga caacctcctc 480
aaagtgggca taccagtttc cacgggggtg ggttgccggg cagagcttaa gaggactagc 540
acctgcaat gcccctcttc actctaaaat gtacactgac tgcttttagag cccttgataa 600
tagtcttatt cccaccacat actaggcact ccataaatat ctggtgaacc ttcacgacct 660
tatcaacttt acaccatat cccagcaaat gccactcatc cccactcttc atagacacat 720
ttgttactct aacctgcctt aggtctcttg tagctccagc tcttttagaga ctcccggaac 780
ccttttatatg gtgcctcagt aaatatgtta ttaatatgtt aatccggaaa aaaaaaaaaa 840
aaaaaaaaaa aaaaaaaaaa aaaaaaaan                                     869

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&lt;210&gt; 289

&lt;211&gt; 1105

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (34)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 289

```

cagaatgtat tcggcagaaa agggactcag gtangcccag cctgggactg agagcagaaa 60
agcattcaag atttgcaggc cttgctatgg atgcgcttaa tcaccatgga ggccagcaat 120
acccatctca gcatggcttt gatattctct acttccctggc ctttaaaaat gacctataat 180
ttttcagttt gctttactat attttataaa gaaaattcta tcttatgggt gattgagcat 240
tgagacttat gaaggcatta ggatagatag ctcaggaatg taaagggtca gaaaagggtc 300
gttttctcag attaacaat atgatggatt ccatggctga ccttggtgct taaaccagga 360
ggtttcaatc tagtcctaga gttgtgtccc tctgaaaggc ccaatgccat gtaactaact 420
ttaaactgga tatatacttt gagccttact taattcacag ataagttgac ttaactcagt 480
atttttattt caattaatga aaacagtcct cttttcaacc ccagggtgct tacattttgc 540
tggctctccc aagtgaccat tgggtggagac caattaatga aggaatgaaa ttcactttat 600
tgggactgtg gtattcaaca gagccacact taaccacttt ttccaatgaa gaatctccag 660
aatgataatg cccaaatatg gatggccaar aagaatttgt atctacggtg tgctttatgt 720
gtttttgaca ctgctgtatt ctgtgtgac aagtgatttg sagctgggtc caatgtkact 780
gagtgttctc aaaratctct agtaactaag tcaacttaat tttcttaagc ctggtattac 840
tatcagcctc acatttacca ctttgattct agttttttaa ctgttcataa cagggcatac 900
cgagggttgg gatgagagcc tacttctac ctcttaaggc actttcctca ttattttgcc 960
atataatctt gaactgcatg ataagctgtt taaatgtcca tgacttctcc cagagcaact 1020
agcaaagtat atgaccattt tgaatagagg ttagtggaag ggaaaatgta gaggttttaa 1080
gttcacagagg taaaaacctc caata                                     1105

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&lt;210&gt; 290

&lt;211&gt; 1982

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 290

187

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tggatccccc gggctgcagg aattcggcac gagcagagac gtggaggcgt gagggagaac 60
atgcttggtta aatatgcagg tagattagga gacaccaaac agagattcag acacagtaag 120
gctgggatga gatcctcgaa gctgtgtttt aacaaactcc actggagagt cccatattcc 180
ctcaaatgtg ggaatcacga ccctgaacca ggttgggcct gaagcagtca actgaattca 240
ctttttcggg tagtaatttg ttcccagggg cagtgcacaac catgatgttc caggtttggg 300
ctggcactct gccttgaacg taggaagctc ttgatgattt gtggaatgaa tttttaaaaa 360
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atltgatatt ttagtatttt ggtgtaaaaa ccaacaggca aactttgccg ggtactgtgt 480
agaaactcga aaatgtgagg ccagtttgta cagttcagag gaaatgcttt aacgtagaat 540
cagatagctg gaagagatct tcgagggaaa gtaagttccc taaagtcaca tctatgtctc 600
ctagctcagt gttctttgtc attgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtgtgtgat 660
tagaaagggc ttcattcata ctttttccct tggacctgga aaaaaaattt tttttatctt 720
ttcaaagtaa atctattgat ttctagtaat catatktgaa tcaatgttaa agcatatata 780
gtcttatatg taaactagat tcttaagatt atktgaacct ttgagatgaa gtttacactc 840
aactaaaatc attccattga ttttattgat taacatcaat cagtatgttt aaagttatcc 900
taagaagcaa tagtttattt ttaaaaacct tgtayagcaa aataacttaa aaccctttgt 960
gatatcatct taccagttta tttggtaaaa acaaacagtt atttgggtatt tgtcagaatt 1020
cttcagtgcc tgctattaca gctattttcc aattactaat ttgattatac tcaactcaagg 1080
cagtgcagaa tcttgaagta ctttttagca gttaaagtaat attgaattgt attgaatagt 1140
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catctgcctt agaacttctg ggacaatcct gattcgagag attctatccc attatttaca 1260
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atlttattat tagattttgt atggtgattt taggctatga aaacatgatc attatatgta 1380
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gaacgatgat cttaaaggca caaacaccac cagccacttt gctaatttct taatagcaga 1740
tttacattgc agcaagaaaa ccacttttta tagtaacatt cagttaaaaa gaactcaatt 1800
cattgttaac ttcttaaaac agaatttgaa ctttatcaac ctcaacgtgt atataaacta 1860
gatagtcttc aatactttat caacctcaac atgtatataa actagatagt cctcaaatac 1920
tgtttgaatt taataaatgt caatttaaaa atttttaaaaa aaaaaaaaaa aaaaaaaaaa 1980
aa

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&lt;210&gt; 291

&lt;211&gt; 2329

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 291

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tttttttact ctagggaaaa cactgacgaa tggtcagagc tcctatcctg atctttttcat 60
caaggcgctt ttcttaataa tatggttcaa ctgtgaatgt agaagtgggg gggagggggg 120
agaaaaagaa aactctggcg ttagaggata tagaaaaata taagtacaat tgttacaatt 180
aacgcagact tcaaaaaaca aaaaatcaca acccaaacaa accaaaattt aaatgatcag 240
aattggcagc acaaaagaaa cgccctctcc tgacttgtat tgtggcagtc tgaacgcccc 300
cagaaaattg tgccaaagag tttagaaaaa taaatatata ataaaagtaa acacatacac 360
acaaaacagc aaacttcagg taactatttt ggattgcaaa caggataatt aaatgttcaa 420
acaatctgat aaaataacca tttggaaact gcttggcctt ctgttctttt atttgattga 480
ctacaatgcg gtattggtct cttgctgcac ttcaaaagca accaacaaaa caaaaacaaa 540
aaaaagtgtg tgtgtgtgaa tacacacaca cactaactag aagtcttgtg atgaaaatgg 600

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## 188

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cacttggaag aggttttatt tttccactga agttgaaggt taataaaatg gtgtcaaacg 660
tcccctgggc acacacttga atattttttt agaagtgtga tgtggatga ttaccataaa 720
tcagacttaa ttattttccc ttttacaagg gaacagggca tcctgaattt tagagccttt 780
cagcaataag aagggatgtt ggtgagcttt gatcctcttt tggttttgca gttgttagga 840
gtttttgctg gcattttgaa tatgctgctt tcagaaaaac caaggaagtt ttaaaattgc 900
ttcctgggtc ttagaggact aaaaacaaga cctcattcc cactttcatt tccactctag 960
caaaaactgg gcttgctgtt ttctccaact cctcgtttat atcctccctt ccatgtccaa 1020
gccttccatt cctaagtggg attggctcag ttttgcccat ccatatggca gcattcttaa 1080
tagctcttgt acagggtatc agatattgtg ccttttggtg ccagggtcaa agtcaagtgc 1140
cgatctatga accagtgtac aaaaaaaaaa aaatccaggt atttgaagga gagacgctcc 1200
attgtgaata aagagctcat accagctcct aagccctatt aagaagaggc ctggtcctct 1260
aatgccttgt ttccatttca gttgttcttt gagagacaga atgatgtact aaccattcgt 1320
gattattaag atagggttgg gtcagggtt agggaggggg cagaaatatt ggggatagaa 1380
aaaaaatctg atcattcctc agtgcaccc atttctgtcc tgtgtgggct gcttagctag 1440
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atgttttgtt ccagggaagc agttgatgag tgctgttact aatgctttct cccagatcca 1560
ttcagtggtg gagaggagga aaatgggctg gttggatgtg gtcttgggtc cttgcagtta 1620
ctctgcactg gttatgcatt taattctcct cttttctagt taaccttttg ccagtgggtt 1680
ttccatagtc tgggtatttg kccttatatc agttatacca cctaaggcaa ctgggtgcaa 1740
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aagaatgtag ttaccgtctg cttgggaaga tgtcagtga aatgtgaaga taatgggcat 1860
cggactaggc tttggtttkc cacaagtggc agctgcctgt atcaattaca tttattaatt 1920
ttgcttttca tttttcccag ttctcctcac ccccccttg ttgaaatgtt ggacttgctg 1980
tcagaggcaa ctgtaatat gccttaggga cttgtggaga aggggaattg ctcagtgtag 2040
tgttttaact ttcagaacca agcaatctat ttactcttac aaatatataa gaagtgtgtt 2100
agtccaactt taagaaaaat ccaaactcat cagcttttga tagcatcttg gtttttgaaa 2160
caacttcaat ctgtaattgg cattcagaat gcccttggca tgccagtctg tgatggcatt 2220
taagacctgt aaaacacttg agcccaactc gattaaccaa aaccgataac caccaccttt 2280
atcttctaaa taaagtccgc tttattttta ttttcaacaa aaaaaaaaaa 2329

```

<210> 292

<211> 2424

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (666)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1757)

<223> n equals a,t,g, or c

<400> 292

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gatcaattct cacttaagag gccataaac aacccaacat gaaaagggtga caagcctggg 60
tttctcccag gataggtgaa aggggttaaaa tgagtaaagc agttgagcaa acaccaaccc 120
gagcttcggg cgcagaattc ttacacttct cttccccctt ccatctcctt tcccccgga 180
aacaacgctt cccttctggt gtgtctgttg atctgtgttt tcatttacat ctctcttaga 240
ctccgctctt gttctccagg ttttcaccag atagatttgg ggttggcggg acctgctggt 300

```

189

```

gacgtgcagg tgaaggacag gaaggggcat gtgagcgtaa atagaggtga ccagaggaga 360
gcatgagggg tggggctttg ggacccaccg gggccagtgg ctggagcttg acgtctttcc 420
tccccatggg ggtgggaggg cccccagctg gaagagcaga ctcccagctg ctacccccctc 480
ccttcccatg ggagtggctt tccatttttg gcagaatgct gactagtaga ctaacataaa 540
agatataaaa ggcaataact attgtttgtg agcaactttt ttataacttc caaaacaaaa 600
acctgagcac agttttgaag ttctagccac tcgagctcat gcatgtgaaa cgtgtgcttt 660
acgaangtgg cagctgacag acgtgggctc tgcattgccg cagcctagta gaaagttctc 720
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ggcaatgatg acattctgaa aagctgcaat acttatacaa taaattttac aattctttgg 2400
aaaaaaaaaa aaaaaaaagt cgac 2424

```

&lt;210&gt; 293

&lt;211&gt; 2160

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (470)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 293

```

gctcgtgccg tggatgcggc tctgcaggat gaagatgaga tacagggtga tgcattcatca 60
tttgaaagca ctgcaaataa gaaatectec tcctcttctc caggaacccc tgcattctcag 120
ctttatccac agtctcgggg gctggttcca aagtaaagcc agcttctctc ctcccagggc 180

```

190

```

ggaaacagca tttgccttct gagagaagag actagcaaaa agctgcagag aggattcggc 240
ccaaactcag aactgttccc ctgaggagaa gcggtggcct ctttgcagat caaccaactt 300
aatctgggtg aacgtgctgt tcctaactct gcactcagcc cctctgggaa acatctttta 360
attagcatct cagaaatgca tgggtaaggt aaagtgcgat agttcaagtg gaaagcaaga 420
gaatgaccag tgaccttgct tccttcccc ttgccttctt ccccccttn ccctgtgctc 480
cctttctctc ctctctcctt ttctagcctg ttcttwacat ggggctccct tcttgttgaa 540
caatagggca gaatcaggrg tcaccttagc aggaccacat ctttggagcc tcgggataaa 600
atgacagtga ggttgaaaag tgaaaaccct aggaacttga ataggtgcct gttctttag 660
ggagaaatga gaaatcgcat ttggatccag gccccagggtg ggcaccatca gcagtcttg 720
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tcattttatg ttggtcatta ggtgaatatt actcattttc cctcaagaga agctcataag 1500
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caggaggtag taagtgaat gtcttagcat tctgcaaaat ggagatctgt tgtccagcgg 1920
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aagaacaaaa cgctaagggt ggtagcctaa gctgattttc tgctgggtac acgtgtctct 2100
cacaccacat ttcctcaaa ctaatctgaa ttctgtaggc taaaaatatt catgtagcaa 2160

```

&lt;210&gt; 294

&lt;211&gt; 1257

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 294

```

tcgaatgtca tcaggaatga gcagctgccc ctgcagtact tggccgatgt ggacacctct 60
gatgagggaa gcatccgggc tcacgtgatg gcctcccacc attccaagcg gagaggccgg 120
gcgtcttctg agagtcaggg tctaggtgct grakygcgca cgraggccga tgtagaggag 180
gaggccctga ggaggaagct ggaggagctg accagcaacg tcagtgaaca ggagacytcg 240
tccgaggagg aggagtccaa ggacgaaaag gcagagccca acagggacaa atcagttggg 300
cctctcccc aggcgaccc ggaggtggca cggctgcccc tcaaaccaac agacaggaaa 360
aaagccccc ggacctggg gaccccgctc agtacaacag gaccacagat gaggagctgt 420
cagagctgga ggacagagt gcagtgcagg cctcagaagt ccagcaggca gagagcgagg 480
tttcagacat tgaatccagg attkcagccc tgaggccgc aggtcacgg tgaagccctc 540
gggaaagccc cggaggaagt caaacctccc gatatttctc cctcgagtgg ctgggaaact 600
tggcaagaga ccagaggacc caaatgcaga cccttcaagt gaggccaagg caatggctgt 660

```

## 191

```

gccctatctt ctgagaagaa agttcagtaa ttccctgaaa agtcaaggta aagatgatga 720
ttctttttgat cggaaatcag tgtaccgagg ctgctgaca cagagaaacc ccaacgcgag 780
gaaaggaatg gccagccaca ccttcgcgaa acctgtggtg gccaccagt cctaacggga 840
caggacagag agacagagca gccctgcaact gttttccctc caccacagcc atcctgtccc 900
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caccctccac atggactccc acctgcaagt ggacagcgac attcagtcct gcactgctca 1020
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taagctgctg tgacttccct ttaggacaat gttgtgtaaa tctttgaagg acacaccgaa 1140
gacctttata ctgtgatctt ttaccccttt cactcttggc tttcttatgt tgctttcatg 1200
aatggaatgg aaaaaagatg actcagttaa caccaaaaaa aaaaaaaaaa gtcgagc 1257

```

&lt;210&gt; 295

&lt;211&gt; 1117

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 295

```

gccctgagcc ccgccatggg ggtgccggag gaccagctga cccgctggca cccgcgcttc 60
aacgtggatg aagtacccca catcgagccg gccgcgctgc cccagccacc cgccacggag 120
aagctcacca ctgctcagga ggtgctggcc cgggcccgcga acctgatttc acccaggatg 180
gagaaggcct tgagtcaatt ggccctgcgy tctgctgcgc ccagcagccc cgggtctccc 240
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aaggggggtgt cccaggatct gctggagcgg atccgagcca aggaggcaca gaagcagctg 360
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gagytggccc gcgtgctgcg gagcgtcttt gtgtccgaac gcaagcctgc gctcagcatg 480
gaggtggcct gtgccaggat ggtgggcagc tgttgtacta tcatgagccc tggggaaatg 540
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tgaatatggg accttccaca gcaaaggggtg acttttg 1117

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&lt;210&gt; 296

&lt;211&gt; 468

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 296

```

tcgacccacg cgtccgccac gcgtccggag gtttttccct tggagggcaa acaaagtggc 60
agtgggggacc aggggtgtccc ctgctgagaa atggagagct cttttccctt gtacttctct 120
gggggtttgcc ttgtggaacc aagtgccttg gggaggagct cctggcagga ctccagctgt 180
tatttgtcag aggacagcta ggattgggtc acccttgctc tgagttggcc ccaaagcgag 240
ctatgctgaa ctcttctcca tctccaagca gacaaccttt gtctttacat gcaagaggga 300
tccaattatg acaggctgac ccagctgggt tcatgttttg ggtttatcta ctgagtaagg 360
ctgaccttac ctgagtttct gtatgtgtat ttgcaagaca gtttaatacta atccatcatc 420
cctcacagag atgtagagga tgagatgtag taacttatag cagtgtca 468

```

192

<210> 297  
<211> 464  
<212> DNA  
<213> Homo sapiens  
  
<220>  
<221> misc feature  
<222> (80)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (458)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (461)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (464)  
<223> n equals a,t,g, or c

<400> 297  
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tcatcataat tgctgaagag atccccctccc ctgcccctgg gttcctgcct tccctcctca 180  
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tgctctcagg cctcaaacc tttcatacct ttattctttt ttttaaccaa aaaagttttt 300  
cttataaaat aaatttttggg caaacawmaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 360  
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 420  
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aggggggncc nttt 464

<210> 298  
<211> 2630  
<212> DNA  
<213> Homo sapiens

<400> 298  
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gagtgccaac gaggaccagg agatggaact agaagcatta cgctctatatt atgaaggaga 300  
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tcccaaagcc ttcttaatag agatttcctg gacagaaaca tatcccaaaa cacctccaat 420  
tctatctatg aacgcttttt ttaacaacac catatcatca gctgtaaagc agagtatatt 480  
agccaagcta caggaagcag tagaagctaa tcttgggaacc gctatgacct atacattggt 540



193

```

tgaatatgcc aaagacaata aagagcagtt catggagaat cacaatccca tcaattccgc 600
aacatcgata agcaatatca tctcaattga aactcctaata acagcccat caagtaagaa 660
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&lt;210&gt; 299

&lt;211&gt; 1422

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (13)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (16)

&lt;223&gt; n equals a,t,g, or c

194

<220>  
 <221> misc feature  
 <222> (1205)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1367)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1381)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1398)  
 <223> nequals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1401)  
 <223> n equals a,t,g, or c

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 gggtagattt ttgagagcat tccaaatgaa tgggtctctg tcaaatgaat gaatggtaa 660  
 atgaataaat ctgccctcac agagatacaa aaggaaaagg aatataattc ataccatttg 720  
 gtttaagcct tacattcatg aagaacctca agggtagatt tttgagatca ttccaaatga 780  
 agtcgaatct gccctcacag agacacaaga aaggaatata attcatacac tattgcattt 840  
 ttaataaatc ttttgaaatt tgcagaatta gattgtattg tgtattttcg gttaaatgat 900  
 aattgaatgt aaatatttag atgcagcacc atattttata acccagcttt agcatttctt 960  
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 atatcatgaa ggtcaattat aattccatat acctttcttt gatgccacag tcagagatag 1320  
 atacagttgg gtggccatgg gtgtgcccat acagacaatt tttggtnaat tgtttcagac 1380  
 nttcaggtct gagactgnca ntgctggggg gcctcctggg tt 1422

195

<210> 300  
<211> 553  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (484)  
<223> n equals a,t,g, or c

<400> 300  
gcccacgcgt cccgatgggtt cttctattca ggcttcaatg gacaggcacc ttcgggatca 60  
aagtacagag cagtcaccat ctgatcttcc tcaaaaggara acagaagttg tgagttcttc 120  
tgcaaagtct gggagtcttc agactgggtt gcctgaatct tttcctttaa ctggtgggtac 180  
tgaaaatttg aatacagaaa caactgatgg ctgtgtagca gatgcaactgg gagcagcctt 240  
tgccacaagg tcaaaagcac aaaggggaaa ttccgtggag gagcttgaag agatggatag 300  
tcaagatgct gagatgacta acacaactga gccaatggat cactcttgat ttaattagag 360  
gctaataaag gcagaatggt tattgtgaat atgtaatat tgttggctgg gccacgtaac 420  
ttgattagtc attaaaaatc ttgtacgtat ataaaaagat tatactctgt tattcagtg 480  
atgntagcaa gtgtgtgatt ggccatagct tttaatatac tgctgcccag gctggctctg 540  
aatttctata aat 553

<210> 301  
<211> 464  
<212> DNA  
<213> Homo sapiens

<400> 301  
ctcaaaaatc accagaaaac tcatactagt gaaaaatcct ataaatgtaa tgaatgtaga 60  
aaggccttta gttactgctc tggctcttatt caatgtcagg tcattcatac tatagaaaaa 120  
ccttatgaat acggtaaatg tggcaaaagcc tttaggcaga ggacagacct taaaaaacat 180  
cagaaaatgc ataccgarga gaaaccctat gaatgtaatg aatgtgggaa agccttttagc 240  
cagagcacat atcttacaaa acaccaaaaa attcatagtg aagagaaatc aaatatacat 300  
actgagtgtg gggaaaccwt twgrcaaaac tcttcttttt tacaacaata aaaacctcac 360  
actggagaga ttctctgaat gccttaagaa tttggttaat atggagaccc ttcccagggg 420  
aaccagaagg aggatcgtga aaacctgttg actacttaga tgat 464

<210> 302  
<211> 2018  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (1997)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (2012)  
<223> n equals a,t,g, or c

196

&lt;400&gt; 302

```

gccacatccc ggcagccctc ctacckgcgc acgtggtgcc gccgctgctg cctcccgcctc 60
gccctgaacc cagtgcctgc agccatggct cccggccagc tcgccttatt tagtgtctct 120
gacaaaaccg gccttgtgga atttgcaaga aacctgaccg ctcttggttt gaatctggtc 180
gcttcgggag ggactgcaaa agctctcagg gatgctggtc tggcagtcag agatgtctct 240
gagttgacgg gatttcctga aatgttgggg ggacgtgtga aaactttgca tcctgcagtc 300
catgctggaa tcctagctcg taatattcca gaagataatg ctgacatggc cagacttgat 360
ttcaatctta taagagttgt tgcttgcaat ctctatccct ttgtaaagac agtggcttct 420
ccaggtgtaa stgttgagga ggctgtggag caaattgaca ttggtggagt aaccttactg 480
agagctgcag ccaaaaacca cgctcgagtg acagtgggtg gtgaaccaga ggactatgtg 540
gtggtgtcca cggagatgca gagctccgag agtaaggaca cctccttga gactagacgc 600
cagttagcct tgaaggcatt cactcatacg gcacaatatg atgaagcaat ttcagattat 660
ttcaggaaac agtacagcaa aggcgtatct cagatgccct tgagatatgg aatgaacca 720
catcagaccc ctgcccagct gtacacactg cagcccaagc ttcccatcac agttctaaat 780
ggagcccctg gatttataaa cttgtgcgat gctttgaacg cctggcagct ggtgaaggaa 840
ctcaaggagg ctttaggtat tccagccgct gcctctttca aacatgtcag ccagcaggt 900
gctgctgttg gaattccact cagtgaagat gaggccaaag tctgcatggt ttatgatctc 960
tataaaaccc tcacacccat ctacgcggca tatgcaagag caagaggggc tgataggatg 1020
tcttcatttg gtgattttgt tgcattgtcc gatgtttgtg atgtaccaac tgcaaaaatt 1080
atttccagag aagtatctga tgggtataatt gcccaggat atgaagaaga agccttgaca 1140
atactttcca aaaagaaaaa tggaaactat tgtgtccttc agatggacca atcttacaaa 1200
ccagatgaaa atgaagttcg aactctcttt ggtcttcatt taagccagaa gagaaataat 1260
ggtgtcgtcg acaagtcatt atttagcaat gttgttacca aaaataaaga tttgccagag 1320
tctgcccctc gagacctcat cgtagccacc attgctgtca agtacactca gtctaactct 1380
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gtgcttttga tgaagtttaa aacaggagtg aagagagcag aaatctccaa tgccatcgat 1560
caatatgtga ctggaaccat tggcgaggat gaagatttga taaagtggaa ggcactgttt 1620
gaggaagtc ctgagttact cactgaggca gagaagaagg aatgggttga gaaactgact 1680
gaagtttcta tcagctctga tgccttcttc cctttccgag ataacgtaga cagagctaaa 1740
aggagtgggt tggcgtagat tgcggctcct cgggttctgc tgctgacaaa gttgtgattg 1800
aggcctgcga cgaactggga atcatcctcg ctcatacgaa cttcggctct tccaccactg 1860
attttaccac aactgtttt ttggcttgct tatgtgtagg tgaacagtca cgcctgaaac 1920
tttgaggata actttttaaa aaaataaaac agtatctctt aatcactgga aaaaaaaaaa 1980
aaaaaaaaaa aaaaccncgg ggggggcccc gnacccca 2018

```

&lt;210&gt; 303

&lt;211&gt; 658

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (621)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 303

```

gacatttagg aacaattgca cttttaaagg gagagaatgc atagttgctc acatatctca 60
gtgtcagtc cctaactagg atcagtgcct tatttgagat tacaaaacta gaaaatgacg 120
gagtcaaggc taggaccaat attctgttca gtcttagata attatagaat acacattaaa 180

```

197

```

atcagatatt tgaattttct taattttgta actatttgtc attgaaagga gatactaaaa 240
aaattatata tcgtcctaga aagtacatga actaataatg catttctaaa ggtgaaaaaa 300
gaataggtat ttttctgttt aatattcaat ttatagagag tagtacgtta atttttttaa 360
acccagaag ctcaggatct tatcatttta aaagaaatta tcaccagttc tgtgtgagta 420
aataaagtat tataacactt tgttttttca tccatgatac cttgtattta cttacctgag 480
ctttttttct agggaaagaa aaatgctcag gtaataacag agccttgaaa aattkggatt 540
ttcaaaacta cctatttatg tataggcctt tagatcatct gatgttgaat actctttaag 600
tgatctaaag gcctacatat naaaagggtat ttttattaaa ttctggatta aacatttc 658

```

&lt;210&gt; 304

&lt;211&gt; 671

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (524)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (593)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (657)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (659)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (671)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 304

```

tttacttaat cttgcctagt cacaaaataa gatgtgcacc catggtttgg agagttccta 60
tattagctga gcagtgagat acactatttc caaacggtgc acacctacag tagctttgga 120
aatgagccaa tcaactgtttt acttaatggt tcttatcagc atgcaaatat tgcttgaaag 180
ttatttcctt attcactggt ttgttagtcc attttgttag gaaacattaa ttcctaaaaa 240
tttgttcaga ataattaaaa gtgaacattt ggtgctgata ctcaaaaacc taaaaatgta 300
gccatttaaa aagtaacatg tttttctccc ctgctcattg cctgggagaa tggaatttta 360
tataactacc tttcttttgca aaaataacgg tcgtgtcgag ttggtggtga ttttggcatt 420
ccatcttgca ctggttttcta gtataggctt agaaataatt ggcaggtaat aatctttcca 480
gtcaagttgc aagggtatgct tatttctctt caaaaaaaga catnctgcgg gattgagtag 540
aaaatttagg tcagtttggg agcttatttg aatattttct actacattgg agntagcagt 600
ctttttctgg atcagatcag tgcattggtt tctacagggt gaatgcttct tgggtgngna 660

```

198

agatctagct n

671

&lt;210&gt; 305

&lt;211&gt; 1680

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 305

```

ccaaagtgct ggaattccag gcatgagcca ctgcgcccag tctacacact aattcttggt 60
agcccaacag ctgttctggt ctatctaccc ctcatltcac gctcaaggag tcatacctag 120
aatagttaca cacaagaggg aaactggaag ccaaacactg tacagtattg tgtagaaagt 180
cacctcccta ctctctttat ttacatgag tgctgatgtg ttttggcaga tgagctttca 240
gctgaggcct gatggaaatt gagataacct gcaaagacat aacagtattt atgagttata 300
tcttagttct tgaaattgtg gaatgcatga ttgacaatat atttttaatt tttatttttt 360
caagtaatac cagtactggt taactatagc cagaactggc taaaattttt atattttcag 420
agttgaagtt ggtgaagaca ttcattgatt aaacaccaga tcctgaaagg ggttaaactc 480
actttgaaat gaatctgcaa tcagtatttc aaagcttttc tggtaatttt agtgatctta 540
tttgattaga ctttttcaga agtactaaat aaggaatttt aacaggtttt tattaatgca 600
cagataaata gaagtacagt gaggtctata gccattttat taaaatagct taaaagtttg 660
taaaaaaatg aatctttgta attacttaat atggttagtta agaaccgctc aagcttatat 720
ttgctagact tacaaattat tttaaatgca tttatctttt ttgacactat tcagtggaa 780
gtgtaagcta gctaattctt gttttctgat ttaaagcact tttaaatctt atcctgcccc 840
ctaaaaacaa aagggttttg tcacaagggg aaatttaaga ttgttaacct tgtttttcag 900
aagggtact gttaattgca cataaacatg aaatgtgttt tccctgtgt actaacacat 960
tctaggcaaa attcaaaact atagtggtaa agaaacagg tgttcacttg ctgagggtgca 1020
aaaattctta agacttctgt ttgaaattgc tcaatgacta ggaaaagatg tagtagttta 1080
ctaaaattgt ttttctacca tatcaaatta aacaattcat gcctttatag ggtcaggcct 1140
acaatgaata ggtatggtgg tttcacagaa ttttaaaata gagttaagg gaagtgatgt 1200
acatttcggg ggcattaggg tagggagatg aatcaaaaaa taccctagt aatgctttat 1260
attttaatac tgcaaaagct ttacaaatgg aaacctgca attacctgcc ttagttcttt 1320
tgtcataaaa acaatcactt ggttggttgt attgtagcta ttacttatac agcaacattt 1380
cttcaattag cagtctagac attttataaa cagaaatctt ggaccaattg ataataattc 1440
tgactgtatt aatattttag tgctataaaa tactatgtga atctcttaaa aatctgacat 1500
tttacagtct gtattagaca tactgttttt ataatgtttt acttctgcct taagatttag 1560
gttttttaaa tgtatttttg ccctgaatta agtggttaatt tgatggaaac tctgctttta 1620
aatcatcat ttactgggtt ctaataaatt aaaaattaaa cttgaaaaaa aaaaaaacga 1680

```

&lt;210&gt; 306

&lt;211&gt; 782

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 306

```

gaattcggca cgagtgaagc attagaatga ttccaacact gctcttctgc accatgagac 60
caaccaggga caagatccca tcccatcaca tcagcctacc tccctcctgg ctgctggcca 120
ggatgtcgcc agcattacct tccactgcct ttctccctgg gaagcagcac agctgagact 180
gggcaccagg ccacctctgt tgggaccac aggaaagagt gtggcagcaa ctgcctggct 240
gacctttcta tcttctctag gctcaggtag tgctcctcca tgcccatggc tgggccgtgg 300
ggagaagaag ctctcatagc ctttccact ccctctggtt tataggactt cactccctag 360
ccaacaggag agggaggctc ctgggggttc ccagggcgag taggtcaaac gacctcatca 420
cagtcttctt tctcttcaa gcgtttcatg ttgaacacag ctctctccrc tcccttgtag 480

```

199

```

tttctgaggg tcaccactgc cagcctcagg caacatagag agcctcctgt tctttctatg 540
cttgggtctga ctgagcctaa agttgagaaa atgggtggcc aaggccagtg ccagtgtctt 600
ggggccctt tggctctccc tcaactctctg aggcctccagc tggctcctggg acatgcagcc 660
aggactgtga gtctgggcas gtccaaggcc tgcaccttca agaagtggaa taaatgtggc 720
ctttgtcttct gttaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 780
aa 782

```

```

<210> 307
<211> 1791
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (487)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (515)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (1769)
<223> n equals a,t,g, or c

```

```

<400> 307
ggggattgtt cctgaaacat tcacgctgtc caatctccca catttcagaa ttgggtgggag 60
tgtgcatttg attgttaata accagctggg ttacaccact ccagctgaaa gaggaagggtc 120
ttctttatac tgcagtgata ttgggaagct tgtgggctgt gccatcatcc atgtcaatgg 180
agacagccca gaggaagtgg tccgtgccac acgactggct tttgaatacc aacgccagtt 240
ccgcaaggat gtgattattg atctgttgtg ctacaggcag tggggccaca atgagctgga 300
tgagccattc tacaccaacc ccatcatgta caaaatcatc agagctcgaa agagcattcc 360
agacacatat gcagagcacc tcattgctgg cggactcatg acgcaggagg aggtgtctga 420
aataaaatcc tcctactatg ccaagttgaa tgatcactta aataacatgg cccactacag 480
gcccccntgc cctgaacctg caggcccayt ggcangggcc tgggtcagcc agaagsgcaa 540
wtcaccacct ggagtacagg tgtgcccctc gacctcctgc ggtttggttg catgragtyt 600
ktagagggtg caagrgagyt gcagwtgcac agtcamctgy tgragacaca tgttcagtcc 660
agaatggaga agatgatgga cggaatcaag ctagactggg ccaccgcgga actcttgcc 720
tgggttcttt acttgctcaa ggttttaatg ttcgtctaag tggccaagat gttggtcgtg 780
gaactttcag tcagaggcat gcaatggtgg tttgccagga gacggatgac acctacatcc 840
ccctgaacca tatggacca aatcagaagg ggtttctaga ggtcagcaac agccccctgt 900
cagaagaggg cgctctggga ttccaatatg ggatgagcat tgagagccca aagttactgc 960
ccctgtggga ggcacagttt ggcgatttct tcaatgggtg ccagatcatc tttgacacat 1020
tcattctctgg aggagaggcc aagtggctcc taaaagcgg cattgtcatc ctccctccac 1080
atggctacga tggggctggg ccagaccact catcctgtcg aatagagcgt ttcctgcaga 1140
tgtgtgacag tgcggaagag ggggtggacg gagacactgt gaacatgttt gtggttcacc 1200
caacaactcc tgcacagtat ttccacttgc ttaggagaca gatgggtccg aacttcagaa 1260
aaccactcat tgttgcttcc cctaagatgt tactcargct cccggcagcc gtgtcaactc 1320
ttcaagaaat ggcaccagga acaacattta acccggtcac tgggtgattca tctgtggatc 1380

```

## 200

```
caaaaaaggt taagaccctc gktttctgct ccggcaaaca tttctactcc ctggtgaaca 1440
aagagaatct ctgggggcca agaagcatga ctttgccatc atccgagtag aggaactctg 1500
ccccttcccg ttggattctt tacagcaaga gatgagcarr tacaaacatg ttaaagatca 1560
tatttggagt caggaggaac ctcagaacat ggggtccgtgg tcgtttggtt ctccaagggt 1620
tgaaaagcag ctggcctgca agctccgtct ggtggccggc cccctttgcc agtaccgct 1680
gtaggaattg gcacagttca cttgcaccag catgaagata tcctcgccaa gaccttcggt 1740
tgatgatgat tttgaaggaa catatttcnt ttaggaatgg cattaggccc t 1791
```

&lt;210&gt; 308

&lt;211&gt; 723

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (705)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 308

```
gggcaagacc tcatgcctaa aaaataaaga gaaagcagag taaaactgga ctctgagata 60
ygactaaagt tctgtgtgat acgtgtgcct tattttagctc aagacattcc tggagcacct 120
ataaaaactg acttgtaatc caggctatgt ctcttttttag cttcgtaatc tttggcaagg 180
ccatttgatt cttcagctgt acaattagga gactcgatca ggtgattgcc tttctcagct 240
gtcagttctc taatttcagg cttggtagct tgtaggaact gaaattgcaa ttaaaacctt 300
tataaactca aactaaatca tgaattacag aaaaagtcca ttcttccaaa acttgatggt 360
accacactta caagtttaaa atatgaagtc gactgtttta aggattctgc atatattcta 420
gtgtgcacat tcagaaacat ttttcttgga aaaagtaccc aacatttttt ataactgcac 480
atattaattt attgccagaa taaattgcat tgcattgctaa ataaagtcag ataattcaaa 540
tccatttgct tttatgtagt ttttcttcta aatgtcaaca ttttggaatt aaaatgttta 600
tggttttata tgagggtagg aaatcttaac tgctttgggg ggtattgttt ataggctttt 660
tgttatgggg ccggtagttt tttaataggg ggattgccc tttcnaccgt ttgggggccc 720
ggg 723
```

&lt;210&gt; 309

&lt;211&gt; 533

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (393)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (396)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (463)



201

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (527)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 309

```
aattcggcac gagcgacgtg gtgctgggcg ttgggaccct actttatcta gttcgggaag 60
ttgggttgtg gggtcatacc tgtctgtctg ctcccagctt tcttgggttt ctcccgacgg 120
cgtggggcct cgctaaggaa ttcccggccc ctccagggcca cggcttttagc ggtgtctttt 180
gcgagtctct cgtaagtaca tcttaaagct gtcaagatgg ttctagcaga ccttgggaaga 240
aaaataacat cagcattacg ctcgttgagc aatgccacca ttatcaatga agaggtatgt 300
aaaatattgt atgraatata tatgattgta ttattgtcac tagcattggg aagatggctt 360
attcataatc cccgtattta tatgtatttt gangtngact taatacttgt gggtaaaagc 420
ccaaaggggt taacagtagg aggggtttat tggggaatta ccnccaactc aaattacttc 480
aaccttcctt aagggatttc ccaaaaaaaa aaaaaaccgg ggggggnccc cga 533
```

&lt;210&gt; 310

&lt;211&gt; 763

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (317)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 310

```
gttttgaata aagaaagaaa agtttactat ctgtatgtag agtgatctta atttgtgatc 60
ctatatatga gacagtataa aaatacagat aagttttaga aagactcaaa acaatatgta 120
aatgactgat gtttgcatta ttaaggaaaa cttgggatgt tgggtcaaga ggggaaagtg 180
ttagtcaatc cactttggag caatatcatg aagggtcaatt ataattccat atacctttct 240
ttgatgccac agtcrgagat asaatacart ttgggtggcc atggatgtgc cccaatacag 300
tacacatttt tkgggttnaaa tttgttttca gatcatttca tggaatcttt gaagtatctt 360
tgactctaac tttgacttgg tgggtggacct tccttgggtt ttataacacc taagagatat 420
cctttagaat tacatgtatt ttagcataag gaaattgaaa aagtaaaaca tactgggttt 480
tttcaacaag accatatgta aattaaatag tgaaatgtgt atgagtttca gtagaactgt 540
accatcaaca atgtttccat aaatatgcag agttctttct tttgtattgt tatttacaat 600
attgttaaag tgaatgcatt tgcaatttct aggattctaa agaattgagt acagaaagta 660
gcaattttat tattttgatga taatatgaga attactgtgc caatactgtt ttgataaata 720
aatagatttt taaaaataaa tgtattgtac ttattagtgt agt 763
```

&lt;210&gt; 311

&lt;211&gt; 3131

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (4)

202

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (5)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (10)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (26)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (3128)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 311

```
gggnncaaan gctggagctc caccgnggtg cgtecgctct agaactagtg gatcccccg 60
gctgcaggat tcggcacgag gccacttctt gggggccgcg gcggggccgc tggctgcact 120
cagcgccgga gccgggagct agcgggccgc gccatgtccc accagaccgg catccaagca 180
agtgaagatg ttaaagagat ctttgccaga gccagaaatg gaaagtacag acttctgaaa 240
atatctattg aaaatgagca acttgtgatt ggatcatata gtcagccttc agattcctgg 300
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ttattcaggt tagattctca gaatgccag ggatatgaat ggatattcat tgcattggtct 420
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aaggaatttg gaggtggcca cattaaagat gaagtatttg gaacagtaaa ggaagatgta 540
tcattacatg gatataaaaa atacttgctg tcacaatctt cccctgcccc actgactgca 600
gctgaggaag aactacgaca gattaaaatc aatgaggtag agactgacgt ggggtgtggac 660
actaagcatc aaacactaca aggagtagca tttcccattt ctcgagaarc ctttcaggct 720
ttggaaaaat tgaataatag acagctcaac tatgtgcagt tggaaataga tataaaaaat 780
gaaattataa ttttggccaa cacaacaaat acagaactga aagatttgcc aaagaggatt 840
cccaaggatt cagctcgtaa ccatttcttt ctgtataaac attcccatga aggagactat 900
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gatgtaatta gaaagatcga gatagacaat ggggatgagt tgactgcaga cttcctttat 1080
gaagaagtac atccaagca gcatgcacac aagcaaagt ttgcaaaacc aaaaggctct 1140
gcaggaaaaa gaggaattcg aagactaatt agggggccag cggaaactga agctactact 1200
gattaaagtc atcacattaa acattgtaat actagttttt taaaagtcca gcttttagta 1260
caggagaact gaaatcattc catgttgata taaagttagg aaaaaaattg tacttttttg 1320
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tctagaaagt ctgatgtctc aaagggtaaa cttactactt tcttgtggga cagaaagacc 1560
ttaaataatt catattactt aatgaatatg ttaaggacca ggctagagta ttttctaagc 1620
tggaacttta gtgtgccttg gaaaaggccg caagttgctt actccgagta gctgtgctag 1680
```

203

```

ctctgtcaga ctgtaggac atgtctgcaa cttttagaaa tagtgcttta tattgcagca 1740
gtcttttata tttgactttt ttttaatagc attaaaattg cagatcagct cactctgaaa 1800
ctttaagggt accagatatt ttctatactg caggatttct gatgacattg aaagacttta 1860
aacagcctta gtaaattatc tttctaatagc tctgtgaggc caaacattta tgttcagatt 1920
gaaattttaa ttaatatcat tcaaaaggaa acaaaaaatg ttgagtttta aaaatcagga 1980
ttgacttttt tctccaaaac catacattta tgggcaaatt gtgttcttta tcacttccga 2040
gcaaatactc agattttaaa ttacttttaa gtcctggtac ttaacaggct aacgtagata 2100
aacaccttaa taatctcagt taatactgta tttcaaaaca catttaactg ttttctaata 2160
ctttgcatta tcagttacaa cctagagaga ttttgagcct catatttctt tgataacttg 2220
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tttatgctgc ataaatcact tatcggaat gcacatttca tagtgtgaag cactcatctc 2400
taaaccttat tatctaagg aatatatgca cttttcagaa atttgtgttc gagtaagtaa 2460
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gaaaatcagt gatgcatttg ttatagagta taactcatcg tttacagtat gtttttagttg 2940
gcagtatcat acctagatgg tgaataacat attcccagta aatttatata gcagtgaaga 3000
attacatgcc ttctggtgga cattttataa gtgcatttta tatcacaata aaaatttttt 3060
ctcttttaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 3120
aaaaaaaaaa a
3131

```

&lt;210&gt; 312

&lt;211&gt; 940

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (135)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (890)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (929)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 312

```

aagcgtgact ctggagatgg agtccaagtt ggcggcagaa aagaaacaga cggaacaact 60
gtcacttgag ctggaagtag cagcactcca gctacaaggt ctggacttaa gttctcggtc 120
tttgcttggc atcgncacag aagatgctat tcaaggccga aatgagagct gtgacatata 180
aaaagaacat acttcagaaa ctacagaaag aacaccaaaag catgatgttc atcagatttg 240

```

204

```

tgataaagat gctcagcagg acctcaatct agacattgag aaaataactg agactgggtgc 300
agtgaacccc acaggagagt gctctgggga acagtcccca gataccaatt atgagcctcc 360
aggggaagat aaaacccagg gctcttcaga atgcatttct gaattgtcat tttctgggtcc 420
taatgctttg gtacctatgg atttcctggg gaatcaggaa aatatccaaa atcttcaact 480
gcgggtaaaa gagacatcaa atgagaatct gagattactt catgtgatag aggaccgtga 540
cagaaaagtt gaaagtttgc taaatgaaat gaaagaatta gactcaaaac tccatttaca 600
ggaggtacaa ctaatgacca aaattgaagc atgcatagaa ttggaaaaaa tagttgggga 660
acttaagaaa gaaaactcag atttaagtga aaaattggaa tatttttctt gtgatcacca 720
ggagttactc cagagagtag aaacttctga aggctcctaat tctgatttag aaatgcatgc 780
agataaatca tcacgtgaag atattgggag ataattgtggc caagggtgaat gacagctggg 840
aaggagagat ttcttgatgt gggaaattga gctgagtagg gtccagatcn ggagaaagct 900
agcctttgag ccttgaagcc ctcttaccng gggaggcttg 940

```

&lt;210&gt; 313

&lt;211&gt; 850

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (848)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 313

```

caaagttgat ttttaacggt tgtaaagggt tgaatgttta tagaagtgca tcatgaaatt 60
ttgtgtaaat ccagatgaac tgtcattata gtactataaa ttagagatag tccataaagt 120
tgggttgaag gagattgaaa atatttcctt tgattaaaag aaaataatta actaacttgg 180
gcttgcttgt gattgaagag ggagattaga tagtcctctg tccccccraa aaagaaacta 240
gcagagaaaag acmtaaaaaaa gctcttttgt gtctgttcat gtgctgtaca ttttttccgt 300
tttaatgtct tgtgtagata attcaaagtt tgaactatct ctttcttgga ataagtaata 360
atattattcaa tatggtgtat ctctgagttc aattttaaac aatccaactc agtaatatct 420
attttttaaat acaaatccta actaaccaat taattaataa aaaggcaaga cttacttgct 480
gtagtatttg ttctcatctg tagagaactg acattggagc aaattttaag tctccccctt 540
gaaaataagc cttgttaact gagggcgtaa tacatttccc acagatttat ccagaaacat 600
tttattagag atcttatagt agtatctcag ttctactac agctttctaa aggatgagac 660
ttgcatttaa caaaatgaca tatataatat ttttctatag ttttgcaact gaattaaagg 720
aagggtgatgt attataatgt gtagtgaggt ataaagggtc agttcattct ctccaacaa 780
gaacttagaa taaaataaca cytttttttc atgagactta cctcattttt ggtaggctat 840
ggcagttntg 850

```

&lt;210&gt; 314

&lt;211&gt; 958

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (930)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

205

<221> misc feature  
<222> (934)  
<223> n equals a,t,g, or c

&lt;400&gt; 314

```
cttgcgctccc cgcgtgtgtg cgcctaattct caggtgggtcc acccgagacc ccttgagcac 60
caaccctagt cccccgcgcg gccccttatt cgctccgaca agatgaaaga aacaatcatg 120
aaccaggaaa aactcgccaa actgcaggca caagtgcgca ttggtgggaa aggaactgct 180
cgcagaaaga agaaggtggt tcatagaaca gccacagcag atgacaaaaa acttcagttc 240
tccttaaaga agttaggggt aaacaatatc tctggtattg aagaggtgaa tatgtttaca 300
aaccaaggaa cagtgatcca ctttaacaac cctaaagttc aggcattctt ggcagcgaac 360
actttcacca ttacaggcca tgctgagaca aagcagctga cagaaatgct acccagcatc 420
ttaaaccagc ttggtgcgga tagtctgact agtttaagga gactggccga agctctgccc 480
aaacaatctg tggatggaaa agcaccactt gctactggag aggatgatga tgatgaagtt 540
ccagatcttg tggagaattt tgatgaggct tccaagaatg aggcaactg aattgagtca 600
acttctgaag ataaaacctg aagaagttac tgggagctgc tattttatat tatgactgct 660
ttttaagaaa tttttgttta tggatctgat aaaatctaga tctctaatat ttttaagccc 720
aagccccctg gacactgcag ctcttttcag tttttgctta tacacaattc attctttgca 780
gctaattaag ccgaagaagc ctgggaatca agtttgaaac aaagattaat aaagtctttt 840
gcctagtata aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 900
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa gggnggccgt tttaaaggaa ccaggttt 958
```

<210> 315  
<211> 500  
<212> DNA  
<213> Homo sapiens

&lt;400&gt; 315

```
cgattgaaca ggagaagcaa gcaggcgaat cgtaatgagg cgtgcgccgc caatatgcac 60
tgtacattcc acaagcattg cttcttatt ttacttcttt tagctgttta actttgtaag 120
atgcaaagag gttggatcaa gtttaaatga ctgtgctgcc cttttcacat caaagaacta 180
ctgacaacga aggccgcgcc tgcctttccc atctgtctat ctatctggct ggcagggaag 240
gaaagaactt gcatgttggt gaaggaagaa gtgggggtgga agaagtgggg tgggacgaca 300
gtgaaatcta gagtaaaacc aagctggccc aaggtgtcct gcaggctgta atgcagttta 360
atcagagtgc catttttttt tttgttcaaa tgattttaat tattggaatg cacaattttt 420
ttaatatgca aataaaaaagt ttaaaaactt aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 480
gcggccgctc gaattaagcc 500
```

<210> 316  
<211> 1228  
<212> DNA  
<213> Homo sapiens

&lt;400&gt; 316

```
ggcacgagct cgtgccgctt gcaactccac ctacagcagt gtctctcagt cctctcaaag 60
caaggaaaaga gtactgtgtg ctgagagacc atggcaaaga atcctccaga gaattgtgaa 120
gactgtcaca ttctaaatgc agaagctttt aaatccaaga aaatatgtaa atcacttaag 180
atttgtggac tgggtgtttg taccctggcc ctaactctaa ttgtcctggt ttgggggagc 240
aagcacttct ggccggaggt acccaaaaaa gcctatgaca tggagcacac tttctacagc 300
aatggagaga agaagaagat ttacatggaa attgatcctg tgaccagaac tgaaatattc 360
agaagcggaa atggcactga tgaaacattg gaagtgcacg actttaaaaa cggatacact 420
```

## 206

```

ggcatctact tcgtgggtct tcaaaaatgt tttatcaaaa ctcagattaa agtgattcct 480
gaattttctg aaccagaaga ggaaatagat gagaatgaag aaattaccac aactttcttt 540
gaacagtcag tgatttgggt cccagcagaa aagcctattg aaaaccgaga ttttcttaaa 600
aattccaaaa ttctggagat ttgtgataac gtgaccatgt attggatcaa tcccactcta 660
atatcagttt ctgagttaca agactttgag gaggagggag aagatcttca ctttctgcc 720
aacgaaaaaa aagggattga acaaaatgaa cagtgggtgg tccctcaagt gaaagtagag 780
aagaccgctc acgccagaca agcaagtgaag gaagaacttc caataaatga ctatactgaa 840
aatggaatag aatttgatcc catgctggat gagagagggt attggtgtat ttactgccgt 900
cgaggcaacc gctattgccg ccgcgtctgt gaacctttac taggctacta cccatatcca 960
tactgctacc aaggaggacg agtcactctgt cgtgtcatca tgccttgtaa ctggtgggtg 1020
gcccgcatgc tggggagggt ctaataggag gtttgagctc aaatgcttaa actgctggca 1080
acataataa aatgcatgct attcaatgaa tttctgccta tgaggcatct ggcccctggg 1140
agccagctct ccagaattac ttgtaggtaa ttctctctct catgttctaa taaacttcta 1200
cattatcacc aaaaaaaaaa aaaaaaaaaa

```

&lt;210&gt; 317

&lt;211&gt; 1731

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1661)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1726)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 317

```

gcaatctttt tctctcctgg ttaaattgggg ctgttgatca ttttctctac gtaagggaat 60
ttattgatta agtttaatta atttgatata gactgtcatg tagtgatgta gtgctatact 120
gtagtcggaa gtttttctta aaagcaaaga gcaaaaatgc aaagttttat ttgtaaaagc 180
tgaggaccct tggggatgga ttaggtttgc cgatgatcct aaaagtaagc aaactgtatg 240
acaagactac tattgcaaat gaaggatatt tatagctaaa ctgcgcacac aaaagaagtt 300
ttatattgtg agttatagtt ggttcagaaa acagtttgta ctctccctgg cccaggaagg 360
cacacagaca aaaatgtcgg ccacttttac tcaaatacag cccaagcaca gacagtcagg 420
ttcgtgatca tcaccaacat ctgataaaat ctcatagaag gcaatgccat cacagctttg 480
ctcaattact acgaggaaga gacaacaagc atctttctgt ttgtctcgtc tgattggagg 540
ctgaatagta gatggaatgg ggggacagtg tgcctgggtg gaggaagacg taagatcccc 600
matttgaaa gcatgcccc ctccctttta gtagaagccc atggttgccc tttgccaaac 660
tggggaggag gcaatgagcc ttggtggaag gaacctctct gtkgatattt aaagaagtga 720
gggctgtggg tattcattgt tagaaatgcc aatttcactt tgaaaccata gtccaagtct 780
ctaggttggg agaagggaaa ggaagggaag ggtcccagtg attctagatc tgggtgggaa 840
acttctgcct catgactctg tcctttgagc ctttgagacag cagcacaata cataacaatt 900
tttattttta aacagaccca ttctttttga tcccacagga gctgtgggtg ggtcgccgtg 960
agccccggga tgtggtttta gtggattact gcctagctga gccaaaatgt ttgcttgtag 1020
ctgttggaac actacagcaa accgctgctt acagtgcatt gtgtatttct gtagtactgt 1080
tttgcatttt ccatagagac agaaaacttt gcaagtcaat cactgttggt cccatggtag 1140
tgtaagaaaa aaaaaaagga aaaagaaaaa aaaaaagaaa accagccaat cattgcgtgt 1200

```

## 207

```

acagagctaa aaattgtaat taatagagcc tgttgggaaa aaaaagaaaa caactgttgc 1260
ctttttttct tgtataaaaag agaatttatg acaaaattta gctgtgagga atgtgatacg 1320
tgtttatatt tctgaatatg gracaaattg attcatgggg atatatattta atgtaaacta 1380
aatcaggatg gtaaagttgt tttaaaatgg grgactatat aagtaattct ctaaagcttt 1440
agttggtttg aatatcatca tttcctccat ggtgagcctg cttgtgratt attaagcact 1500
tgtttgcatc ctctgttctt cactcattta tttcttgcag tgtgctatgg acttaatgct 1560
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ataaatatta cattgttcat agctttatgt gacttatggg nttatacata acattagaat 1680
gagtaagctg tagttgtgtg gacattttat aaaaacaaaag gtcccnttcc c 1731

```

&lt;210&gt; 318

&lt;211&gt; 1208

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (29)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 318

```

cgggtcgacc cacgcgtccg gaaagatcnt ctttaggaat aatagatgat ggtaagttcc 60
acttttggtta ttggaaggca agtcattatt actggtatta gttaaaacac atatcaaag 120
cttgctcttc atcatatata tagttatgca tacatacaca cacacacata cagtatattc 180
tttcctcaaa agggtttaaga tgtctaaaat agggacctag aagcttaaca ctatttaagt 240
aaatacagta gaagctcaca aatagatttc tttgcacaat gattttttgc aaaattttac 300
agtaataata atcccaaggc aaatctctcc tgaactgctt tccattccat aatttgtagt 360
ataattcttg gattccactg tttcttttgg ggaatggaag ttctgaatta aaagcccact 420
gtggagatgc tgtggttcat ggaatctctt ccagtgtaat tcagaatcat tggcctagaa 480
agtctctgat atttggaggg gaacaaaaat cactcacaag caatccatga tctatacaca 540
taagcataat ttccttttagt tctagttagt catcagagaa cagtcagtga tgcaagtttt 600
gtgactgaga aatttctgtg ctccaatcc acaatgagat gcatgatttt gttttcatcc 660
catttcccc cagcccctgt aaatcagggg aaatgcgcaa ctgatcgctt aggagagggc 720
ctcgtagtgg cacagctgga gatagtttca aagtctaaac caccagccca tcctgaggaa 780
agcctcctat ggaatgtaaa gtgcaatcat ttcttcagat ataagacttt cccaacaat 840
gtgattggat tcctttatgg caaaatcgag agaagctgcc atccacctgc ttatgcattt 900
atctcttttg tggacttgtc tgaccacctt ctatttgccc agagtttgct caattccaag 960
acagtgccca tgaatgggac acctgtaatg taaccacac agcggtttgc agagaatgtt 1020
agccatgact tgggctttct gaaagttggc tataatttct ctatccctac ccacaacct 1080
gggaagtttg agcaagaggg gcatactatt gggctgggag gatttgacag catttcccc 1140
gttgcccttt aagttcttct atttcaaacg ttaattttgc ttctctttct aaaaaaaaaa 1200
aaaaaaaaa 1208

```

&lt;210&gt; 319

&lt;211&gt; 756

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (30)

208

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 319

```
ccccagtcctt accactctag catgcttgtn ataataaaca tggtagtgga cttttttcta 60
aagatccccc ctctctcaga ggtcatgtcc ttctgtaacc agcccttgct cttgaacccc 120
cakgcagttt ggtgggttatg ccaaggaagc agactacgta gcacaagcca cccgtctgcg 180
tgctgccctg gagggcacag ccacctaccg gggggacatc tacttctgca cgggttatga 240
ccctcccatg aagccctacg gacggcgcaa tgagatctgg ctggtgaaga catgagtga 300
ccactgaacc aagaacttac tggaagtgtg cctctgtgtc tccttcctcg ggggtaagga 360
ggggacagtg cttcccaagt tccagctgca agtccaactt aaccaacttt cttcaaaagt 420
cagttactgc caattttctg aaaaaagcat gttccatata ctaagtctct tttctcacgg 480
taggaaataa tacagccaag atatgcagca tccttctcat tgatgtagaa aattctgcga 540
tagaccagaa aaatcctggc agcttttctc caggcatctg ggtcactaaa aactgatttt 600
ctaaaattat tggatttgta ttttgttatt aagggggaaa atgtgatttg tgcctgatct 660
ttcatctgtg attcttataa gagctttgtc ttcagaaaaa ctaaaaataa aaggcattga 720
cttaaacagc tgaramaaaa aaaaaaaaaa aaaaaa 756
```

&lt;210&gt; 320

&lt;211&gt; 1209

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1203)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 320

```
cttcgccgtc atccgcttcg aaagcatcat ccacgagttc gaccgcgtgg ttaactatag 60
atcaacacat catcttgcat ctcatgggtt ctatgaattt ttaaattggg ttgatgaaag 120
agcatgggat ccactaggaa gaatagtagg tggtagtggt taccagggtg tgatgataac 180
cgctggcctt attcattgga ttttaaatac attgaacata actgttcaca taagagacgt 240
atgtgtgttc cttgcaccaa cttttagcgg ccttacatct atatctactt tcctgcttac 300
aagagaactt tggaaccaag gagcaggact ttttagctgt tgttttattg ctattgtacc 360
aggctacata tctcggtcag tagctggatc ctttgataat gaaggcattg ctatttttgc 420
acttcagttc acatactatt tatgggtaaa atctgtaaaa actgggtcag ttttttggac 480
aatgtgctgc tgcttatcct atttctatat ggtctctgct tgggggtggg atgtatttat 540
catcaatctt attccactgc atgtatttgt gttgttactg atgcagagat acagcaaaag 600
agtctacata gcatatagca ctttctacat tgtgggttta atattatcaa tgcagatacc 660
ttttgtggga ttccagccaa tcagaacaag tgaacacatg gcagctgcag gtgtctttgc 720
attgctgcaa gcttatgctt tcttgagta tctgagagac cgattaacaa aacaagagtt 780
ccagaccctt ttcttttttg gtgtatcact agctgcaggg gctgtgttcc ttagtgtcat 840
ctatttgact tatacagggt acattgcacc atggagtggc aggtttttatt cattgtggga 900
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gacttgggtg tctttcttct ttgatctaca tattcttgta tgtaccttcc cagcaggcct 1020
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actactttga tatggaatag ttatttttct ttttgagatt atttacttta aatttttgtt 1140
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tanccaaga 1209
```

&lt;210&gt; 321



209

<211> 668  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (653)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (654)  
<223> n equals a,t,g, or c

<400> 321  
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ctggatgatg tttatgacgg gtacgtaaatt ttctgaagrt tctttcttcc aaaacatggt 120  
gaatttgtac aacttctctg ccaagggttat ggctgaccag ctccgcaage ctcccagccg 180  
agaccagtgg agcatgaccc cccagacagt gaatgcctac taccttccaa ctaagaatga 240  
gatcgtcttc cccgctggca tcctgcaggc ccccttctat gcccgcaacc accccaaggc 300  
cctgaacttc ggtggcatcg gtgtgggtcat gggccatgag ttgacgsatg cctttgatga 360  
ccaagggcgc gagtatgaca aagaagggaa cctgcggccc tgggtggcaga atgagtcctt 420  
ggcagccttc cggaaccaca cggcctgcat ggaggaacag tacaatcaat accaggtcaa 480  
tggggagagg ctcaacggcc gccagacgct gggggagaac attgctgaca acggggggct 540  
gaagctgcct acaatgctta caaagcatgg ctgagaaagc atggggagga gcagcaaytg 600  
cagccgtggg ggttamcaac caccastytt cttcgtggga ttgccccag gtnntggtgc 660  
tcggtccg 668

<210> 322  
<211> 809  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (372)  
<223> n equals a,t,g, or c

<400> 322  
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ttacatattt aacaaacctt gaagctaaat cagtttgtct tttatcaaaa ctgcaactcc 180  
tctaagttga aagcacagtg acaagagaaa gcattacaaa ttcttgagaa ataatagaaa 240  
ttaaagctct tttcaaacct gtgaacaagt atagtaccag aagtataaga ttcagatagg 300  
cccaagttgt agttcttggt atgagtctta caaccctatg gactttggac aaattacttc 360  
tctgcgtctg tntcctcatc tgtaaaatga aaataatttc tgtttcatac aggtatagtc 420  
taaataggga taattacacc tacttcaaag ttgtaaaata cacaattaca actagatagg 480  
aggtataagt tctagtgttc tgtagcactg taggatgact atagttaaca atattgtata 540  
gtttcaaaata gctagaagaa ggatattgca tgttcccaaa acaaagacat aagtttttga 600  
gatgatagat atgctaatta ccctaatac tatatgttat atgtattgca acatcactat 660  
gtacccccat aaatatgtac agttattgtg tattaaaatt tttttaaact aaaattataa 720

210

gacattaaaa aaaggtatca catgtaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 780  
aaaaaaaaaa aaaaaaaaaa tcgagggggg 809

<210> 323  
<211> 1442  
<212> DNA  
<213> Homo sapiens

<400> 323  
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tgccctggacc cagagtgtgg gggaaatatc tctggagaag cctcactcc aaaggctgtc 120  
caggcgcaat gtggtggctg cttctctggg gagtccctcca ggcttgccca acccgggggt 180  
ccgtcctctt ggcccaagag ctaccccagc agctgacatc ccccggttac ccagagccgt 240  
atggcaaagg ccaagagagc agcacggaca tcaaggctcc agagggttt gctgtgaggc 300  
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tgagctgggg atgggggggg tcccgccagg actgtggcca gggagattcc cgggggtgtg 420  
ggaagtggcg gtgccctgaa tccccatctt ggaggaggga tgaattttcc atgtaggggc 480  
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cacatattgg ttgttaaaaa tatgtcatca tgtatttgtt gagtgcctgc tctatcaggt 720  
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gagctattac aaaacttcta acgccaagc cttattcaga ataaggacat tttaaaaaca 840  
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gaggatcaga gggctggagc ccagggttca aggccagcct aagcaacata gcaagacccc 960  
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attttattta tatcaaaatg acataaattt ttgaacttta ttttttaatt ttaaaatttt 1080  
taattattat ggatacataa tagttgtaag actttttgtt ttttaattaa agttttctaa 1140  
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cgctgaagtg agaggatcac ttgagcctgg aaggtagagg ctgcagtgag ctctgatcat 1380  
gacaccgtac tccagcctgg gtgacagagt gagaccctgt ctccaaaaaa aaaaaaaaaa 1440  
aa 1442

<210> 324  
<211> 2701  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (1)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (9)  
<223> n equals a,t,g, or c

<220>

211

&lt;221&gt; misc feature

&lt;222&gt; (17)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2699)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 324

```
ncattcatnt tttcaangct cgtgatctca cggcccggtc gccggccccc gctctgccct 60
gcagcataat aaaatggcta atcaggtgaa tggtaatgcg gtacagttaa aagaagagga 120
agaaccaatg gatacttcca gtgtaactca cacagaacac tacaagacac tgatagaggc 180
aggcctccca cagaagggtg cagaaagact tgatgaaata tttcagacag gattggtagc 240
ttatgtcgat cttgatgaaa gagcaattga tgctctcagg gaatttaatg aagaaggagc 300
tctgtctgta ctacagcagt tcaaggaaaag tgacttatca catgttcaga acaaaagtgc 360
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tactctggat gtaaccacag gacagaggaa gtatggtggt cctccaccag acagtgtgta 540
ctctggcggt caacctggaa ttggaacgga ggtatTTgtg ggcaaaatac caagggattt 600
atatgaggat gagttgggtgc cctTTTTtga gaaggccgga cccatttggg atctacgtct 660
tatgatggat ccactgtccg gtcagaatag agggatatgca tttatcacct tctgtggaaa 720
ggaagctgca caggaagccg tgaaactgtg tgacagctat gaaattcgcc ctggtaaaca 780
ccttgaggatg tgcatttctg tggcaaacaa cagacttttt gttggatcca ttccgargaa 840
taagactaaa gaaaacattt tggagaattt cagtaaagtc acagagggtt tgggtggacgt 900
tattctctat catcaaccgg atgacaaaaa gaagaatcgg gggttctgct tccttgaata 960
tgaggatcac aagtcagcag cacaagccag acgccgggtg atgagtggaa aagtaaaagt 1020
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catggctaag gtaaaagttt tgtttgtgag aaacttggct actacggtga cagaagaaat 1140
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kgccgctcmt kagaactagt ggatcccccg ggctggcagg attwcggcac gagaatgaat 1260
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aggaaagagc gccaaagctgc tagacaggcc tccagaagca ctgctatga agattattac 1380
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ggttatgatt atcacgacta tcgtggaggc tatgaagatc cctactacgg ctatgatgat 1560
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agggggaggg gagcaccacc tccaagaggt agagctggct attcacagag gggggcacct 1680
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cgtggttccc gtggatctcg gggcaatcgt gggggcaatg taggaggcaa gagaaaggca 1800
gatgggtaca accagcctga ttccaagcgt cgtcagacca acaaccaaca gaactggggt 1860
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tgcagaacct ttggTTTTgg acagtttcat ttttttggat ttgggataga ttacatagga 2340
gtatggagta tgctgtaaat aaaaatacaa gctagtgtt tgtcttagta gttttaagaa 2400
attaaagcaa acaaatTTaa gttttcttgt attgaaaata acctatgatt gtatgttttg 2460
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## 212

```

cattcctaga agtaggttaa ctgtgttttt aaattgttat aacttcacac ctttttgaaa 2520
tctgccctac aaaatttggt tggcttaaac gtcaaaagcc gtgacaattt gttctttgat 2580
gtgattgtat ttccaatttc ttgttcatgt aagatttcaa taaaactaaa aaatctattc 2640
aaaaaaaaaa aaaaaaaatg accctcgaga aaaaaa aaaaaa aaaaaaana 2700
a 2701

```

&lt;210&gt; 325

&lt;211&gt; 1070

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (9)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 325

```

gtgaaaggng catttgctat acagaccttt agaacagcaa catggagtca ttcctgatcg 60
ggatgcagaa ttttgtcttt ttgacctgtg tgtaaatgtg agagaaaact tctcagttcc 120
agttggcctt cgaggcacca tcataggaat aaaaggagct aatagagaag cccgatgtact 180
atltgaagta ttatttgatk wagaatttcc tggagggtta acaataagat gctcacctgg 240
tagaggttat cgactgccaa caagtgcctt ggtgaacctt tctcatggga gtcgctctga 300
aactggaaat cagaagttga cagccatcgt aaaaccacaa ccagctgtac atcaacatag 360
ytcaagttca tcagtttctt ctgggcattt gggarccctc aaccattccc ctcaatcact 420
ttttgttctt actcaagtac ctactaaaga tgatgatgaa ttctgcaaca tttggcagtc 480
cttacaggga tctggaaaga tgcaatactt cgagccaact atacaagaga aggggtgcagt 540
tctacctcaa gaaataagcc aagtaaatac acatcataaa tctggcttta atgacaacag 600
tgtaaatat cagcaaagaa aacatgaccc tcacagaaaa tttaaagaag agtgtaagag 660
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gaacttttta gcatctttga atatctccaa agaaaatgaa rtacagtcac ctcatcatgg 780
ggagcctcca agtgaagagc atttgtcacc acagtcattt gccatgaagg gaacacggat 840
gcttaaagaa attctaaaaa ttgatggctc taacactgtg gaccataaga atgaaatcaa 900
acagattgct aatgaaatcc ctgtttcctc taacagaaga gatgaatatg gattaccctc 960
tcagcctaaa caaaataaga aattagcatc ttatatgaac aagcctcaca gtgctaataa 1020
gtaccataat gttcagtcct tggacaatat gtgttggcct gccccagcc 1070

```

&lt;210&gt; 326

&lt;211&gt; 1729

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (125)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 326

```

cacagacgct actctgtagc atctcaggtt ccctctggct gcactctgga ggaccacact 60
cgttttcttt ttggctgcca gaggcccccg catccaccgc tgagctggga gaaagatggc 120
ggcancgtgc gacaggattt ggcccagctc atgaattcga gcggctctca taaagatctg 180
gctggcaagt atcgtcagat cctggaaaaa gccattcagt tatctggagc agaacaacta 240

```

## 213

```

gaagcttttga aagctttttgt ggaagcaatg gtaaattgaga atgtcagtcct cgtgatctcg 300
cggcagtttgc tgactgattt ttgcacacat cttectaact tgcctgatag cacagccaaa 360
gaaatctatc acttcacctt ggaaaagatc cagcctagag tcatttcatt tgaggagcag 420
gttgcttcca taagacagca tcttgcatct atatatgaga aagaagaaga ttggagaaat 480
gcagcccaag tgttggtggg aattcctttg gaaacaggac aaaaacagta caatgtagat 540
tataaactgg agacttactt gaagattgct aggcctatct tggaggatga tgatccagtc 600
caggcagagg cttacataaa tcgagcatcg ttgcttcaga atgaatcaac caatgaacaa 660
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gaagctgcac aaaggtacaa tgagctctct tacaagacaa tagtccacga aagtgaagaa 780
ctagaggcct taaaacatgc tttgcaactg acgatcttag catcagcagg gcagcagcgt 840
tctcggatgc tagctactct ttttaaggat gaaagggtgcc agcaacttgc tgcctatggg 900
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ttgtagtcat gtaaaactta agtgcttcat gcctctccaa atgtggttat tctaataaat 1680
ggagaaatga gccaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1729

```

&lt;210&gt; 327

&lt;211&gt; 686

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 327

```

ggcagcagca tgagccactg caccagccg atactactat atccccattt tacagatgag 60
cacatgggca aattgagggt aaggcactga cccatgatca tacagctgag aagtggcaaa 120
ggcaggattt gaacctagaa cctctggctc cacacactag taatctaaac cactctccct 180
acaatacaac atacgtggta aagatgtgtg gtgggcacgc aatcaacgta ggctccctca 240
cagttgctgg gagaggcagg aatttgacgt tcctccgcgt tctctctctc cgctgcccac 300
ctgtcctggg tcattcctgc agcctgccct gccctgacct gtctcacctt cctctgcca 360
acagaagtct gggcagggtt ttatgggctc tgataaggcc ctggcagggc cgaagttcat 420
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tggtcaccag ggaagctggc aagggaaggg agactagggt gcgctctagg agaagccgac 540
agcctgagag tcccagaaga ggagccctgt ggaccctccc ctgccagcca ctcccttacc 600
ctgggtataa gagccaccac cgctgccat cgcgccaccat ctcccactcc tgcagctctt 660
ctcacaggac cagccactag cgcagc

```

&lt;210&gt; 328

&lt;211&gt; 1241

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 328

214

```

agacgagcgt ggcggccgcg gctgctcggg gccgcgctgg ttgccattg acagcggcgt 60
ctgcagctcg cttcaagatg gccgcttgct cgcattcatt ttctgctgaa cgacttttaa 120
ctttcatgtt cttttccgcc cgcttcgatc gcctcsggcc ggctgctctt tccgggattt 180
tttatcaagc agaaatgcat cgaacaacga gaatcaagat cactgagcta aatccccacc 240
tgatgtgtgt gctttgtgga ggggtacttca ttgatgccac aaccataata gaatgtctac 300
attccttctg taaaacgtgt attgttcggt acctggagac cagcaagtat tgtcctattt 360
gtgatgtcca agttcacaag accagaccac tactgaatat aaggtcagat aaaactctcc 420
aagatattgt atacaaatta gttccagggc ttttcaaaaa tgaaatgaag agaagaagg 480
atttttatgc agctcatcct tctgctgatg ctgccaatgg ctctaataag gatagaggag 540
agggtgcaga tgaagataag agaattataa ctgatgatga gataataagc ttatccattg 600
aattctttga ccagaacaga ttggatcggg aagtaaaca agacaaagag aaatctaagg 660
aggaggtgaa tgataaaaaga tacttacgat gccagcagc aatgactgtg atgcacttaa 720
gaaagtttct cagaagtaaa atggacatc ctaatacttt ccagattgat gtcattgatg 780
aggaggaacc tttaaaggat tattatacac taatggatat tgcctacatt tatacctgga 840
gaaggaatgg tccacttcca ttgaaataca gagttcgacc tacttgtaaa agaatgaaga 900
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cagtaaatgg gtcattcagc acttcttctg gttgatacct gagactgtta aggaaaaaaa 1200
aaaaaaaaa accccggccg ctcccacttc agattggtaa c 1241

```

&lt;210&gt; 329

&lt;211&gt; 1652

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 329

```

tctgactgga ctttctatta gctcaactcc accagctgtc agtagtggtc tcagtacagg 60
tgtaccaaca gtaccgttat tgccaccaca agtaaaccag tccctcactt ctgtgccacc 120
aatgaatcca gctactacat taccagggtc gatgccttta ccagcaggac tgcccaacct 180
ccccaacctc aacctcaacc tcccagcacc acacatcatg ccaggggttg gcttaccaga 240
acttgtaaac ccaggctctg cacctcttcc ttccatgcct ccccgaaact tacctggcat 300
tgcacctctc cccctgccat ccgagttcct cccgtcattc ccttgggtc cagagagctc 360
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```

215

```

actttttttc ttgtgttaca tctaaattac aacccttaat tgccacgtgt gcacttacta 1440
ctctccagta tgtcttatta ctctccagta tgtcacgcat ctttaacttt tcacgtccta 1500
tgtttgcttt ctcccatttt taagagatgg taagttaact ggaattgatt tactgaatga 1560
aattaaatgc agatatccct gtttttgaaa taaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1620
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aa 1652

```

&lt;210&gt; 330

&lt;211&gt; 1916

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1895)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1902)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 330

```

gccacggcac gcagccagca agttgttttt aaatgttaat atagaaaaca gtgaaggatt 60
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aaccataaga agaattgtta tcagcacgtt catttattat tttggatttg gaacttggtt 1740

```

## 216

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 attttacttt aaaatgagaa tctgggtgtta ctgtatttta tcgttttcaa taaaactttct 1860  
 taagtgtttt ggaaaaaaaa aaaaaaaaaa aattnctgcg gncgcgaagg gaattc 1916

&lt;210&gt; 331

&lt;211&gt; 1658

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 331

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 ccccgcgccg cggccgcagg gccatgctag ccttgccggt ggcgcgcggc tcgtgggggg 180  
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 aatgaatcca ggttccaata tcaacaaaca ttgctatg 1658

&lt;210&gt; 332

&lt;211&gt; 1102

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 332

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 agtccattgg caagtttggc ctggccttag ctggtgcagg aggcgtgggtg aactctgcct 180  
 tatataatgt ggatgctggg cacagagctg tcatctttga ccgattccgt ggagtgcagg 240  
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217

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&lt;210&gt; 333

&lt;211&gt; 4201

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (4077)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (4161)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (4186)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 333

```

gcggaacgct gggcggacgc gtgggtscgg acgcgtgggc tcgcggcgcc gcctcctgct 60
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gctccccata ctagtccgag atatttggag ttcttacaac atggcagaca ttgacaacaa 180
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218

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aaataaagac aaaacttgaa gtaactgaaa atcttatcgt gctatgtaga aatattgaac 4020

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## 219

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taatattcaa atatttgaat gcttttggtt cagggattgg tttaaaattg gagtcnnttt 4080
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aaatgttatt ttaaattgtac nggaatwga ttgggtagggt gcmggnagga rtgtwagggt 4200
c 4201

```

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<210> 334
<211> 1239
<212> DNA
<213> Homo sapiens

```

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gcaaacttag ttctggtgat ttcttgatgg tttggaagtc tattgctggg aagaaattcc 600
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gcccctactt ttcaacaatt ttctatgta gttgtgaaga actaagggtg ggagcagtag 720
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<210> 335
<211> 1249
<212> DNA
<213> Homo sapiens

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<220>
<221> misc feature
<222> (36)
<223> n equals a,t,g, or c

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<400> 335
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agtttttgat cctgttgaac ccgcctgaga cggtgctgtg aggggaaagc cttccgcacc 180
cacacaggaa ttctgctgag gtcccccttc cttccggcca atggcagaag tgggggaaaa 240
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tgagtattta tctttttatt ttttattttt ttttttgaaa gaatgtcttg gaatgcgcaa 360
gtctcccttt agagccgtct tttgcaggga gcgggaagtg acaagagctc agatctccct 420

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## 220

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tttctgtctt ccaacctcta ctgtaaaact tctggtccga gaacgagccg aacacagcgc 720
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ttaaatttgt atcaactaga aataaaattg catgagtatt ttaaaaaaa 1249

```

&lt;210&gt; 336

&lt;211&gt; 722

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (690)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (703)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (718)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 336

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tttcatcatt catgtaacat tctcacacag ttgaggrtat tcatctcctc accaattcca 180
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aatagacatt gagaggttat atatgtccaa aactcatctg tccagcagtc accgtcctct 600
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ac

```

&lt;210&gt; 337

221

&lt;211&gt; 2210

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (40)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 337

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gcagggtctcc cgagggcaga aggtgaccag cctaacggcc tgcctagtgg accagagcct 240
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&lt;210&gt; 338

&lt;211&gt; 741

&lt;212&gt; DNA

## 222

<213> Homo sapiens

<220>

<221> misc feature

<222> (581)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (656)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (711)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (719)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (720)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (737)

<223> n equals a,t,g, or c

<400> 338

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<210> 339

<211> 2045

<212> DNA

<213> Homo sapiens

223

&lt;400&gt; 339

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2040
aaaaaa 2045

```

&lt;210&gt; 340

&lt;211&gt; 2074

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 340

```

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224

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&lt;210&gt; 341

&lt;211&gt; 2867

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 341

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225

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&lt;210&gt; 342

&lt;211&gt; 2131

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 342

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aaggcagaaa aaggaggctaa aactcaggct atacttttgg agatggtggg agacctacct 720

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226

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tycttgatgg acaaatttgg gttaatgggt t 2131

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&lt;210&gt; 343

&lt;211&gt; 559

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (534)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (539)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (556)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (559)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 343

227

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&lt;210&gt; 344

&lt;211&gt; 2623

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (547)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2623)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 344

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ccacatcatt tggcatcaga gwtgaaaagg atctagggct ggttkttctc agaaccaaga 540
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ccacaagcgt aaggcatatg tcaattgcct ctggacactg gttattttat gtttcagtc 1440

```

228

```

ctaaaaaatg aaatggaaaa aagtgggtgct aaatcgagtc agagatatta caggagagtt 1500
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caagccagag cccccaagg taccagactc ttcttactac acaggtaacta acaggctggc 1620
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gacacactaa ttatgggaag cagaattact ggctgatggc ccctgagggt gtgtgtaaca 2040
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cccaaaaaaa aaaaaaaaaa aaaaaaaaaa aaataaaaaa atn 2623

```

&lt;210&gt; 345

&lt;211&gt; 1843

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1405)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 345

```

ggcacgaggt ggccttgtgg caaacacaaa cgcgttctga tcttcccttc ctacatgaca 60
acagtgattg actacgtgaa gccctcggat ctcaagaagg acatgaacga gaccttcaag 120
gagaagtttc ctcacattaa gctgacactc agcaaaatta ggagtctgaa acgagagatg 180
cggaacttgc gcaggaggac tgtggccttg aggagccac ggtggccatg gcctcgtcta 240
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ggcatgtgtg ctgttagcag ccagcaaaat ttggaagtga cctcaaaaaa cacgagtcaa 360
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```

229

```

tctagatgat ttctggataa gaattgctct ctcggtacca gacagtttga catcctccac 1200
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gcgagttctg agtgttggat gagtcaagtc cgtggaagga cgtggagcgt ggcgctctgt 1320
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gaggcatgtc accacactgt cgcctcatag ctgcaagaga gaggcaccag ctgaagttcc 1740
cctgactgaa gagagcctgt ggccatgtaa aaagagaatt aaactcttgt tgctttttgt 1800
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa 1843

```

&lt;210&gt; 346

&lt;211&gt; 884

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 346

```

ggtgtgagcc actgtgccc gacgtttccc agaatatatt taaatgcaaa gttacatgag 60
gggaaaaacat gtatgtttgc tcctgttggt actgggtagg ttctgaacag cagaaacca 120
tgtgcagggt gggctgggtga agggccctct ccgcaagggt gtagcaggaa aaggctcttg 180
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atggatataa aaaaaaaaaa aaaaaaaacc tcggggtcgg gggt 884

```

&lt;210&gt; 347

&lt;211&gt; 391

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (360)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (381)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 347

## 230

```

ggcacgaggc  ggcatcctgc  tccgtctgca  ggttggtgctt  ccggtgcgga  ggtcagggac  60
aagatggtgc  caccggtgca  ggtctctccg  ctcatcaagc  tcggccgcta  ctccgccctg  120
ttcctcggtg  tggcctacgg  agccacgcgc  tacaattacc  taaaacctcg  ggcaagaag  180
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gaattggcag  aagatgacag  catattaaag  tgagtgaccc  tgcgaccac  tctttggacc  300
agcagcggat  gaataaagct  tcctgtgttg  tgtgataaaa  aaaaaaaaaa  aaaaaacyn  360
gggggggggc  ccgwwacca  nttygccaa  a  391

```

&lt;210&gt; 348

&lt;211&gt; 2540

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 348

```

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tgggaggaac  ttggatgaaa  gccagagcag  agtggccaaa  agaacagttt  attccaccat  180
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```

## 231

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aatttttgtc attaaatggt atattatttc acatatataa aacagatggt atgtaagaat 2400
gttggtatatt ttaacataaa tcatttagag aaattatcta gattcattaa ttttcatagt 2460
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aaaaaaaaa aaaaaaaaaa 2540
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<210> 349

<211> 1926

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (97)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (281)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (302)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (326)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1879)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1885)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1891)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1892)

<223> n equals a,t,g, or c

## 232

&lt;400&gt; 349

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gggggtgggg gacggacaag ccccgatgcc ggggganacg gaagagccga gacccccgga 120
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gnaaggccga gtatccccgc cgccgnagga gcagccccag cgccaggcct cccgacgtcc 360
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gacaggaaga cttggggcat gggacagctc agactttgta tttaaaagtt aaaaaggaca 1860
aaaaaaaaaa aaaggggcng gccgnttcta nnaggatcca agctttacgt accccgttgc 1920
aatgcc 1926

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&lt;210&gt; 350

&lt;211&gt; 1233

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1222)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 350

```

tcctgcatgc acagttgcag ttagttattc caggtattat ttttgttttc agaaaaagaa 60
aactcagtag aagataatgg caagtccaga ctggggatat gatgacaaaa atggctcctga 120
acaatggagc aagctgtatc ccattgccaa tggaaataac cagtcccctg ttgatattaa 180
aaccagtga accaaacatg acacctctct gaaacctatt agtgtctcct acaaccacgc 240

```



## 233

```

cacagccaaa gaaattatca atgtggggca ttccttccat gtaaattttg aggacaacga 300
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ttttcactgg ggcagtacaa atgagcatgg ttcagaacat acagtggatg gagtcaaata 420
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cccaaagctg cagaaagtac ttgatgccct ccaagcaatt aaaaccaagg gcaaacgagc 600
cccattcaca aattttgacc cctctactct ccttcccttca tccctggatt tctggacctt 660
ccttggtctt ctgactcatc ctctcttcta tgagagtgtg acttggatca tctgtaagga 720
gagcatcagt gtcagctcag agcagctggc acaattccgc agccttctat caaatgttga 780
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aaaaaaaaac cccggggggg gnccccgtcc cca 1233

```

&lt;210&gt; 351

&lt;211&gt; 2510

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2503)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2509)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 351

```

gcggacgcgt ggggaaggac agcagagctg acagtcacag cagccctgac aagagagttc 60
ctggagccca agctcttctc cacagaggac aagcaggcag cagagaccat ggggtccctt 120
tcagcctgtc catacagagt gtgcattccc tggcaggggc tctgtctcac agcctcgctt 180
ttaaccttct ggaacctgcc aaacagtgcc cagaccaata ttgatgtcgt gccgttcaat 240
gtcgcagaag ggaaggaggt ccttctagta gtccataatg agtcccagaa tctttatggc 300
tacaactggt acaaagggga aagggtgcat gccaaactatc gaattatagg atatgtaaaa 360
aatataagtc aagaaaatgc cccaggggccc gcacacaacg gtcgagagac aatatacccc 420
aatggaaccc tgctgatcca gaacgtcacc cacaatgacg caggawtcta taccctacac 480
gttataaaag aaaatcttgt gaatgaagaa gtaaccagac aattctacgt attctcggag 540
ccaccaagc cctycatyac cagcaacaac ttcaatccgg tggagaacaa agatattgtg 600
gttttaacct gtcaacctga gactcagaac acaacctacc tgtggtgggt aaacaatcag 660
agcctcctgg tcagteccag gctgctgctc tccactgaca acaggaccct cgttctactc 720
agcgccacaa agaattgacat aggaccctat gaatgtgaaa tacagaaccc agtgggtgcc 780
agccgcagtg acccagtcac cctgaatgtc cgctatgagt cagtacaagc aagttcacct 840
gacctctcag ctgggaccgc tgcagcatc atgattggag tactggctgg gatggctctg 900
atatagcagc cttggtgtag tttctgcatt tcgggaagag tgactggact ggattcttct 960
agctccttca atccccattt ctctgtggc atcactaagt ataagacctg ctctcttctt 1020

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234

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gaagacctat aagctggagg tggacaactc aatgtaaatt tcaaggaaaa accctcatgc 1080
ctgagatgtg ggccactcag agctaaccac aatgttcaac accataacta gagacactca 1140
aattgccaac caggacaaga agttgatgac ttcattgctgt ggacagtttt tcccaagatg 1200
tcccaagcct catcgtgacg aggtctttat cccactccat ttttccctgc tcatgcctgc 1260
ctctttaatt tggtaagata atgctgtaac tagaatttca caatcagcgc cttgtgcagg 1320
taatttgaca gagtggtgga tgtgtcatgt catcatgtca aacccaaata tttgacctaa 1380
gggatccttt attctgcccc gtggctaact ttaacaacat ccctaataca actgtttatt 1440
caaatgcacg gtggctccctg ttagagttag acctctagac tcacctgttc tcacgccttg 1500
ttttaattta acccagctat gggatgccag ataacagaat tgctgcctac tagctgaaca 1560
gggaggagtt tgtgcagttg ctgacacttc ttgttgacac taaataaata cagtgggtac 1620
tatagagact cagttgcaaa aattaacaaa tatgctgctt gattaaaatg ggtaggcttc 1680
tcatgtggct cattctttta tctattctct tttatttggg ttggttcatg gggctctctgc 1740
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ctgggtgtgt gtattctcta aaacctttta atgtttgcat gcagccattc gtcaaatgtc 1860
aaatattctc tctttggctg gaatgacaaa aactcaaata aatgtatgat taggaggaca 1920
tcataacctt tgaatgatgg aagtccaaaa tgatggtaac tgacagtagt gttaatgcct 1980
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tctgctttta ctcttagaaa aaagtaatat gaagtattct gaaattaacc aatcagttta 2220
tttaaatcaa tttatttata ttcttctgtt cctggattcc cattttacaa aacctactgt 2280
tctactgttg tattgcccag taggagctat cactatattt tgcagaatgg aaactgcctt 2340
gactcatgaa tcacaaataa aagccaattg tatctataaa aaaaaaaaaa aaaaaaaaaa 2400
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2460
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aangggggnc 2510

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&lt;210&gt; 352

&lt;211&gt; 2765

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2758)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 352

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gcgagcga cagcgggggc ccgcgtgtc tgggcggccc caggggctgt cggtcactt 60
ccgggaacgc cggggaaccg cagtagccgc ctgctagtgg cgctgctagc cggccgggcg 120
aggctgccga gcgggtgagc gcgcaggcca ggccaaagcc ctggtaccgc cgcggtgcgg 180
gcctcagtct gcggccatgg gggcgtccgc gcggctgctg cgagcgggtg tcatgggggc 240
cccgggctcg ggcaagggca ccgtgtcgtc gcgcactact acacacttcg agctgaagca 300
cctctccagc ggggacctgc tccgggacaa catgctgcgg ggcacagaaa ttggcgtgtt 360
agccaaggct ttcattgacc aagggaact catcccagat gatgtcatga ctcggtggc 420
ccttcatgag ctgaaaaatc tcacccagta tagctggctg ttggatgggt ttccaaggac 480
acttccacag gcagaagccc tagatagagc ttatcagatc gacacagtga ttaacctgaa 540
tgtgcccttt gaggtcatta aacaacgcct tactgctcgc tggattcatc ccgccagtgg 600
ccgagtctat aacattgaat tcaacctcc caaaactgtg ggcattgatg acctgactgg 660
ggagcctctc attcagcgtg aggatgataa accagagacg gttatcaaga gactaaaggc 720
ttatgaagac caaacaagc cagtcctgga atattaccag aaaaaagggg tgctggaaac 780
attctccgga acagaaacca acaagatttg gccctatgta tatgctttcc tacaactaa 840

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235

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agttccacaa agaagccaga aagcttcagt tactccatga ggagaaatgt gtgtaactat 900
taatagtaag atgggcaaac ctccatagtc ttgcatttag aagctgcttt tcctaagact 960
tctagtatgt atgaattcct tgaaaattat attactttta tttctactga ttttattttg 1020
gatactaagg atgtgccaaa tgattcggat actaagatgc atcgtttgaa atcatctagt 1080
gtgttgatag cagttatcct caaaaacatc agcgatgtct gaaccttta aacatctgtt 1140
agagcaaaat taaaagagca tttggtagta atctaacttt ttgttcagtt aataagtggg 1200
tgataaagtt tccatatttt tctggaaaag ttaaaaaaag ttacatgtca tttggagaaa 1260
atacgtaatc agaaatttgt gcatagattg atgccaaaaa agacatttcc agcattgtgg 1320
aacatgggtga gacactatat aaaattccag aaagaaagca actggattta cagatttatt 1380
gtgagacaca aattcactgc tgcctttaca ctaagaaatg tatatgttaa ccatatatgc 1440
tgtattttatt ttgtcgttaa gcatactttc agtttactca gaattttcaa tttgctataa 1500
agatgtatca attagcatat agaaaaatat tactttaaga tgacttgttt cctttgaaaa 1560
tacctgtgta ctgaggggta tgatttgtgt caaaaattga cataagtgtt tttacaagca 1620
ccaaagttga atgaattttc aacaaaatgt aattaaagtc tatgttttca gttatgactc 1680
aggttaagaa atgtgtttta ggatctactt gctgggtttt ctttttgatc caaatgtgtg 1740
atctgccctg ataaataaca agttatagta ccatctcccc cgccaataaa aaagagaaga 1800
aaaaagagaa acccgtggca ctatgtaaat aaagtaagca tactttgttg ttagtaataa 1860
gatgaggcat gcctgggaaa tgctcccttg gcataaatag caatcaatta taattagtaa 1920
acaggtgtac caataaaaag aatttacatg ataggttaac aaggaccagg aaagtgaagt 1980
tcctgaagga gttctttgtt cctgatcaaa gaaattgata cctgttagca ttcactgcca 2040
ccatatttta aggagaaaga actctatttg tgctgtctga gcagccattt aaaaattgga 2100
atctaaagga tggttgctga tgtactgtgt ggtctggtag aagtggggaa atatgagaga 2160
tgaggagaaa acttgattat gtcttccatg gcataattac tcttacttta cttcgtgcca 2220
aatcaaataa aacaagccgt cttacaagtc gttattgcct ttaaaaatct gttccgtttt 2280
tttcccaggt acttaaaata caagtgccag taagtgggtc ttatgtgttt tggggggaaa 2340
attttatttc ctttttcttc tgatatttaa aaaattcatc gatctttcaa gatgaaccaa 2400
ggttttttta aagaawtata ggaaacactt cattctttat aaaactttct ataatgcctt 2460
atltgaatgt taatcttatg tgctttctaa aaaatgttgt gaaataccaa acttatggat 2520
tatcactagg ttatcaagca tatattagtc tttatcagaa taaaatgaaa tttcataact 2580
gtggctatta ctttgttctt ggtccttcac agggcctgct ccatcccacc ttcctttctg 2640
ctgcctgatg tctcaatggc ttctgaatga ctgttctaataaatgatcctt aaaacagaaa 2700
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaanaa 2760
agaga 2765

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&lt;210&gt; 353

&lt;211&gt; 1755

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (134)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (140)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 353

ggcttccggg cccctgagac tggggcctcg ctgcctcccg acccggttgc aagtgttgcg 60

236

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gtgggagaaa gtcgcgctccg catcggaggg gaagcgccgt catgcctaag tattatgagg 120
acaagccgca ggcngcgcn tgcgcggggc tgaaggagga cctgggcgcg tgtctgctgc 180
agtcggactg tgtggtccag gaaggaaaat cacctcggca gtgtttgaag gaaggatact 240
gcaactcttt gaagtacgca ttttttgagt gtaaaagatc agtggtggat aacagggcaa 300
gattcagagg aagaaaagga tattgatgca ttatgttgaa gccaacatgg aaaacaacaa 360
atattttccc tggtcattaa cacaaagaag ccaaacaggg aaacatactt tttactacat 420
ctgtttgggt ggaccagatt tcccctccgt ggaacactga agaaagtga tgagttgttt 480
tcgaatatgt ataaagtaaa tgattctctt gatccaagtt atttttagaa gaaaaacct 540
attgaacagg tatgggttgg gagcataata aatgtgtttt gagaattgtt ctaaagcaca 600
gaaaatggaa agactgttat ttgcaaactt gactcttcaa ttgrattacc caattagtag 660
aggccactga tttgactgac acagtcgata acatgcagcc tatccagaag gtgtctgttg 720
ggaaagttaa ggataaaact tttcttttag ttcagtcttt tcctgtctag ttctaaaatg 780
aattgtgttt gattccttag agaagaaata cttcatttgt gctctgattc actgaagtaa 840
taacctcagc actttaatag cgtccacagg catagctgat gctaggcccc agattgtgtt 900
gccaggctc tttaccatca tcttcggact gttttgttt cctggttaca ttttcagtct 960
ggcccgctct acataatggg ccagtgtcag ctccaagtcc acatccttat tatccatgat 1020
tcaaaaggga gagagagaac ttcctttttc aggggtccaca aatcaaactt ataaaaggac 1080
tctggtcttc ccaggatcac ctgcccttgc attggaccag tccctgtgga agaggggatg 1140
ggggcctgtg atcttggcca ggcctgggct atctatctgc actgtcattg ctaactcctg 1200
tcagaatcac atggatgagt agtgggctga atcccaaaaag gaaaggggtt tagagcaagt 1260
ggaaacaaca gatgttcaat atagaaagca agaagtaaaa ccatgaagtg gttgaagatt 1320
agccttacag taattttatt ctgatcactt aatacagtag agtcaaacag gaatccaagt 1380
ttccaacttt attatttttg gcactgaaga attacaaaga actctagcgt ctttatacct 1440
ccgtggttca ctggagttaa agcaatcggg gcgttggtaca gctcacttga gtttttaaag 1500
gttctactaa aaagttagaa ttccacagca atatgggtca ttgttgacga atatcacaaa 1560
ggtctgttgt gtatactcct tttcaccagg aaagggacaa taatagtttt tttcaatgta 1620
tatatatata agtgatctaa ctttttatta ataaaagtaa acaactctaa aatgtatatt 1680
ataaagccct gtcacttttg ttgagtaata gctttattga gctttatttg gagaaatata 1740
cataccgtaa aattc 1755

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&lt;210&gt; 354

&lt;211&gt; 1959

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 354

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gcaggccagc cccatgggga agcgcagacg ccggmgcctg ggcgctctga gattgtcact 60
gctgttccaa gggcacacgc agagggattt ggaattcctg gagagttgcc tttgtgagaa 120
gctggaaata tttctttcaa tccatctct tagttttcca taggaacatc aagaaatcat 180
gaacaacttt ggtaatgaag agtttgactg ccacttctc gatgaagggtt ttactgcaa 240
ggacattctg gaccagaaaa ttaatgaagt ttcttcttct gatgataagg atgccttcta 300
tgtggcagac ctgggagaca ttctaaagaa acatctgagg tggttaaaag ctctccctcg 360
tgtaccccc ttttatgcag tcaaatgtaa tgatagcaaa gccatcgtga agacccttgc 420
tgctaccggg acaggatttg actgtgctag caagactgaa atacagttgg tgcagagtct 480
gggggtgcct ccagagagga ttatctatgc aaatccttgt aaacaagtat ctcaaattaa 540
gtatgctgct aataatggag tccagatgat gacttttgat agtgaagttg agttgatgaa 600
agttgccaga gcacatccca aagcaaagtt ggttttgagg attgccactg atgattccaa 660
agcagtctgt cgtctcagtg tgaaattcgg tgccacgctc agaaccagca ggctcctttt 720
ggaacgggag aaagagctaa atatcgatgt tgttggtgtc agcttccatg taggaagcgg 780
ctgtaccgat cctgagacct tcgtgcaggc aatctctgat gcccgctgtg tttttgacat 840
gggggctgag gttggtttca gcatgtatct gcttgatatt ggcggtggct ttctggatc 900

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237

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tgaggatgtg aaacttaaat ttgaagagat caccggcgta atcaaccag cgttggacaa 960
atactttccg tcagactctg gagtgagaat catagctgag cccggcagat actatgttgc 1020
atcagctttc acgcttgcag ttaatatcat tgccaagaaa attgtattaa aggaacagac 1080
gggctctgat gacgaagatg agtcgagtga gcagaccttt atgtattatg tgaatgatgg 1140
cgtctatgga tcatttaatt gcatactcta tgaccacgca catgtaaagc cccttctgca 1200
aaagagacct aaaccagatg agaagtatta ttcattccagc atatggggac caacatgtga 1260
tggcctcgat cggattgttg agcgctgtga cctgcctgaa atgcatgtgg gtgattggat 1320
gctctttgaa aacatgggag cttacactgt tgctgctgcc tctacgttca atggcttcca 1380
gaggccgacg atctactatg tgatgtcagg gcctgcgtgg caactcatgc agcaattcca 1440
gaaccccgac tccccacccg aagtagagga acaggatgcc agcaccctgc ctgtgtcttg 1500
tgctgggag agtgggatga aacgccacag agcagcctgt gcttcggcta gtattaatgt 1560
gtagatagca ctctggtagc tgtaaactgc aagtttagct tgaattaagg gatttggggg 1620
gaccatgtaa cttaattact gctagttttg aaatgtcttt gtaagagtag ggtcgccatg 1680
atgcagccat atggaagact aggatatggg tcacacttat ctgtgttcct atggaaacta 1740
tttgaatatt tgtttttatat ggattttttat tcaactcttca gacacgctac tcaagagtgc 1800
ccctcagctg ctgaacaagc attttagtgc tgtacaatgg cagaatgggc caaaagctta 1860
gtgttgtgac ctgttttttaa aataaagtat cttgaaataa ttaaaaaaaaa aaaaaggggg 1920
gccgccctag ggggttcccaa gtttacgtac gctgcatgg 1959

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&lt;210&gt; 355

&lt;211&gt; 1067

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 355

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aattcggcac gaggtcactg ctggctgagg ctgcgctcag gcccgtggat ctcacgaag 60
atggcggcgc gatctgtgtc gggcattacc agaagagtct tcatgtggac agtctcaggg 120
acaccatgta gagaattttg gtctcgattc agaaaagaga aagagccagt ggttgttgag 180
acagtagaag agaaaaagga acctatccta gtgtgtccac ctttacgaag ccgagcatac 240
acaccacctg aagatctcca gagtcgtttg gaatcttacg ttaaagaagt ttttggttca 300
tctcttccta gtaattggca agacatctcc ctggaagata gtcgtctaaa gttcaatctt 360
ctggctcatt tagctgatga cttgggtcat gtagtccta actccagact ccaccagatg 420
tgcagggtta gagatgttct tgatttctat aatgtcccta ttcaagatag atctaaatct 480
gatgaactca gtgccagtaa tctgcccccc aatttgaaaa tcaactggag ttactaagca 540
attcgggaaga gaaacacatt gaaatcactg tctttccctg agcaaggggg ctgctcatta 600
gatcttttga tactttacca tgtgaaatac taccagaact gttctctaaa cccacttttt 660
ctgtagagga atgtatcatc ttttttttcc tcatattaca aatggacaaa taacggactt 720
tctattttca tatttgctga aaccattttt taaatgaaat taggtcatta tttatgaaaa 780
gttttgagag ggcactgtca acttgggttt aagacaggag gacattgcaa gttcacacct 840
ttcataagca taaagtagtt gcaagaaagt attttcatcc tgtaggatt catatctaag 900
atagagttat gcattgcaca tacacaaata aacttttatt agatagatac ctataaaaga 960
aacataaaag tatgttgtgt attactgaca gttctagatt aatttctttt agaattaaag 1020
tagatttgtt aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa 1067

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&lt;210&gt; 356

&lt;211&gt; 1023

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

238

&lt;222&gt; (996)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (998)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1003)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1016)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 356

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cctagtgcgt agcgccccggc tcctgcaggc gctcggcctc cgctcattcc tgacccccgca 60
gtgggcgcga tggcgaggagc tgtactgagg gtcgccccggc ggcagctgag ccagcgcggc 120
gggtctggag cccccatcct cctgcggcag atgttcgagc ctgtgagctg caccttcacg 180
tacctgctgg gtgacagaga gtcccgggag gccgttctga tcgaccagc cctggaaaca 240
gcgcctcggg atgcccagct gatcaaggag ctggggctgc ggctgctcta tgctgtgaat 300
acccactgcc acgcggacca cattacaggc tcggggctgc tccgttcct cctccctggc 360
tgccagctctg tcatctcccg ccttagtggg gcccaggctg acttacacat tgaggatgga 420
gactccatcc gcttcgggag cttcgcgttg gagaccagg ccagccctgg ccacacccca 480
ggctgtgtca ccttcgtcct gaatgaccac agcatggcct tcaactggaga tgccctgttg 540
atccgtgggt gtgggcggac agacttcag caaggctgtg ccaagacct gtaccactcg 600
gtccatgaaa agatcttcac acttcaggga gactgtctga tctaccctgc tcacgattac 660
catgggttca cagtgtccac cgtggaggag gagaggactc tgaaccctcg gctcaccctc 720
agctgtgagg agtttgtcaa aatcatgggc aacctgaact tgcctaaacc tcagcagata 780
gactttgctg ttccagccaa catgcgctgt ggggtgcaga caccactgc ctgatctcac 840
ttctgtcaga tgctcccatc cactattaat gcactagggt ggaggagagg gcggcaatga 900
cactgcacct ctcttttccc accgcattcc ctggagctcc ctaaataaaa ctttttttaa 960
cgtgaaaaaa aaaaaaaaaa aaaggggggg ccgctnangg ggntcaaatt ttaggnacgg 1020
ggg 1023

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&lt;210&gt; 357

&lt;211&gt; 1953

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (45)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (47)

239

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1686)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1821)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1920)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1927)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1935)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1948)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1951)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 357

```

gtcacgagcg aggggggtgcg tgtgaggtca tcgcgcgggc gggcntncgg ggtctggcgg 60
tttgaacgag acgaagacgg aaccggagcc gggtgcgggc agtggacgcg gttctgccga 120
gagccgaaga tggcagtga cgtatactca acgtcagtga ccagtgataa cctaagtcga 180
catgacatgc tggcctggat caatgagtct ctgcagttga atctgacaaa gatcgaacag 240
ttgtgctcag gggctgcgta ttgtcagttt atggacatgc tgttccctgg ctccattgcc 300
ttgaagaaaag tgaaattcca agctaagcta gaacacgagt acatccagaa cttcaaaaata 360
ctacaagcag gttttaagag aatgggtggt gacaaaataa ttctgtgga caaattagta 420
aaaggaaaagt ttcaggacaa ttttgaattc gttcagtggt tcaagaagtt tttcgatgca 480
aactatgatg gaaaagacta tgaccctgtg gctgccagac aaggtcaaga aactgcagtg 540
gctccttccc ttgttgctcc agctctgaat aaaccgaaga aacctctcac ttctagcagt 600
gcagctcccc agaggcccat ctcaacacag agaaccgctg cggctcctaa ggctggccct 660
gggtgtggtgc gaaagaaccc tgggtgtgggc aacggagacg acgaggcagc tgagttgatg 720
cagcaggtca acgtattgaa acttactgtt gaagacttgg agaaagagag ggatttctac 780

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240

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ttcggaaagc tacggaacat tgaattgatt tgccaggaga acgaggggga aaacgaccct 840
gtattgcaga ggattgtaga cattctgtat gccacagatg aaggctttgt gatacctgat 900
gaagggggcc cacaggagga gcaagaagag tattaacagc ctggaccagc agagcaacat 960
cggaattctt cactccaaat catgtgctta actgtaaaat actccctttt gttatcctta 1020
gaggactcac tggtttcttt tcataagcaa aaagtacctc ttcttaaagt gcactttgca 1080
gacgtttcac tccttttcca ataagtttga gttaggagct tttaccttgt agcagagcag 1140
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ccaccangcc aggtngattc catgcctngc naa 1953

```

&lt;210&gt; 358

&lt;211&gt; 2026

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (701)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 358

```

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tggccctgtc agtggctctc ttggccctcc tgaaatggta ctccacatca gcattctcaa 300
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```



241

```

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gccaaaaaaa aaaataagaa gaaaatgaaa aaagttttgc gtcgac 2026

```

&lt;210&gt; 359

&lt;211&gt; 1799

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 359

```

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```

## 242

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<210> 360

<211> 510

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (417)

<223> n equals a,t,g, or c

<400> 360

```

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cctttttacc tctgtgtaaa aaatatatat acaagtgtat gatgtacatt ttagttctta 300
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tgtaaataata aacacatcct atgcaraaaa aaaaaaaaaa aagggcggcc gctctanagg 420
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```

<210> 361

<211> 1087

<212> DNA

<213> Homo sapiens

<400> 361

```

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tggtctcttt tagggtaaga agtttgtgtc tttgtctggc cacatcttga ctaggtattg 180
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gagcggaaact atgaaaagtg ggcttgagga tggcaggaga gcttgtcatt gagcctggca 420
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aattgtgtat tttctttggg ggtggaaaag gaaaacaatt caagctgaga aaagtattct 1020
caaagatgca tttttataaa ttttattaaa caattttgtt aaacaaaaaa aaaaaaaaaa 1080
aaaaaaaaa                                     1087

```

<210> 362

<211> 2273

243

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 362

```
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atccgcttgc tgctcgccga cccgccgctt atgcacaagt acgaggagtt catgctgcgc 240
cgctacctag cctcggaccc cgactgccgc tggtgcccg ccccggaactg cggttatgct 300
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ggcagcaatc catgaggtgt gtcaaagagt gtacatatgt atgtgtgtat attgaatgct 2160
aaacatatta ctgaaagaca cattttaata aagatttctg tcataattca aaaaaaaaaa 2220
aaaaaaaaaa aaaaaaaaaa aaaaaaaagg ggccgctcgc gatctagaac tag 2273
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&lt;210&gt; 363

&lt;211&gt; 1848

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (976)

244

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1845)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 363

```
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caacttgtgg gtttgttctg tttttccatg agaataaaat actggcggtt tttttcaaaa 1800
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa agggngga 1848
```

&lt;210&gt; 364

&lt;211&gt; 1808

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1808)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 364

245

```

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aaaaaaaaan

```

&lt;210&gt; 365

&lt;211&gt; 1280

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 365

```

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gacagggcaa ggcccagggt gagattgtca ctgatgggga ggagcctgct gagatgatcc 720
aggtcctggg ccccaagcct gctctgaagg agggcaacct tgaggaagac ctcacagctg 780

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246

```

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gttcaataaa  ggagacaagt  gctttcccaa  aaaaaaaaaa  aaaaaaaaaa  aaaaaaaaaa  1260
aaagaaaaaa  aaaaaaaaaa  1280

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&lt;210&gt; 366

&lt;211&gt; 2138

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 366

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gatttcaggg  gaagattgat  gctgcttatt  ttgagaccag  caaataacctg  ttggatgttc  60
tcaataaaaa  gtacagcttg  ctggaccaca  tgcaggcaat  gaggcggtac  ctgcttcttg  120
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247

attaaaagca attatctttc agatgcaaaa aaaaaaaa

2138

&lt;210&gt; 367

&lt;211&gt; 3179

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (475)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2488)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (3178)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (3179)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 367

gcttccagct	gagatcccat	cgggacatgt	ttctagtgtc	cttcagttcc	tagcattccc	60
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cagcccasga	gagccatagc	agctgctggt	gccaccgttc	agcaggggtg	agtgccctgc	180
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248

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaann 3179

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&lt;210&gt; 368

&lt;211&gt; 1826

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1799)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 368

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tccccggggc tgcaggaatt cggcacgagg tggattcttg tccatagtgc atctgcttta 60
agaattaacg aaagcagtggt caagacagta aggattcaaa ccatttgcca aaaatgagtc 120
taagtgcatt tactctcttc ctggcattga ttggtggtac cagtggccag tactatgatt 180
atgattttcc cctatcaatt tatgggcaat catcaccaaa ctgtgcacca gaatgtaact 240
gccctgaaag ctacccaagt gccatgtact gtgatgagct gaaattgaaa agtgtacca 300
tggtgcctcc tggaatcaag tatctttacc ttaggaataa ccagattgac catattgatg 360
aaaaggcctt tgagaatgta actgatctgc agtggtcat tctagatcac aaccttctag 420
aaaactccaa gataaaaggg agagttttct ctaaattgaa acaactgaag aagctgcata 480
taaaccacaa caacctgaca gagtctgtgg gccacttcc caaatctctg gaggatctgc 540

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249

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agcttactca taacaagatc acaaagctgg gctcttttga aggattggta aacctgacct 600
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ttaaatcact cgaatacctt gacttgagct tcaatcagat agccagactg ccttctggtc 720
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aatggcaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaanc 1800
ccccgggggg gggcccccct cccctt                                     1826

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&lt;210&gt; 369

&lt;211&gt; 839

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (112)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (179)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (809)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (829)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (831)

250

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (837)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 369

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tagtcatgga ggatttggta tgacttgacc acaggtttag accaaggctg agaagaacag 60
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acaagattca tctattttaa gaaatgttgg tgttctaata caaagcatta ttttactna 180
gagaaaatta cttacttgct cccttctgta ttgtaatatt ttgtattaag acatgattta 240
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gtattttaac tctggcaaag gttatagaaa gaaaaatggr aatatggtag gcctgtggta 360
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caccagtagt tagctttcta gctgggggag aagacaggag atttttcttc cacagatggt 480
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ctcactaagc tgctgcacac cagctttgcc tgcatgattc aaatttgtgc ctcagtaaaa 600
ttataaatta ttgcatgtca taccttgaat aatggaaacg gcaaacatta aacctgtgat 660
tacccataat gtactttaat aataaaaaac atggcagcca ggtgcagtag agtgcacctg 720
tggtcaggag gctgaagtgg gaagattgct tcaacctgtg agtttgagtc ccgcctggtc 780
aacagcgaga ccccatgtgt ctgctgctnt ctcttttttt aaaggacana ngcttanct 839
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&lt;210&gt; 370

&lt;211&gt; 2315

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1259)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1261)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1299)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2300)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2304)

251

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 370

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tcagcactca aaaagttttg gattttgggg tatttcagat tttagatttt tgtatgagga 60
atgttcaacc tgtatttgaa caagcattac caaatatcat tgaatattaa tatcttttgc 120
gtaaaaactg ctattatcag catcatagtt tctctaaaaa gaaaacttgg ggatcatagc 180
cgatagagag acttgctaaa atataaatca gcctctgcaa aactgtttac atattttattg 240
gtttacatat tttattgggt tattttctatc ccctgttcac tttttctctt ccacttccaa 300
ttatgaagag aaaatatttg ttcagggttg tccccccgcc ccccgctcact gcataatttc 360
tcctcttaca agctgctttt ggctttcatt aataacagct tcctttttaga aggtctgata 420
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gatatttttt waagcactac tcatatcctt taactaaatt ttgccaagcc sgasacaaca 540
ttaaggagaa attgtacctt aagttagtaa ttccaaatct atctgagttg tatacccatc 600
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aactttatat cttgggactt atgtatatat atacctttta aataaaataa attttctaaa 2280
taaaaagtta aaaaaaaaaa gggnggccgc cctag 2315
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&lt;210&gt; 371

&lt;211&gt; 3007

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2984)

252

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2988)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (3002)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 371

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gccactcccc catcgtgggg cagctgcggc tgagggctgt ggctttggca gctgcgacgg 60
ggagcggcgg agaccgcctc tgctcccgcc tgggggttgc gcttttgctc agaggacatc 120
catgacccta atgggtctttt tgttcaagat aaagtgattt tttgcctttg ttgattaact 180
ggrcaaattm agcatgtaga gcratgaag tacaggacaa taaagcttcc tacacatatc 240
accaggagga tctctttgaa agattcactg caggactacc agagagaata atttgtctga 300
agcatcatgt gttgaaacaa cagaagtcta ttcacctgtg cactaactag aaacagagtt 360
acaatgtttt caattctttg agctccagga ctycagggaa gtgagttgaa aatctgaaaa 420
tgcggccatg gactggttcc tggcgttgga wtatgctcat tctttttgcc tgggggacct 480
tgctgtttta tatagggtgt cacttggtac gagataatga ccatcctgat cactctagcc 540
gagaactgtc caagattctg gcaaagcttg aacgcttaaa acagcagaat gaagacttga 600
ggcgaatggc cgaaatctct ccgataacca gaaggcccta ttgatcaggg gccagctata 660
ggaagagtac gcgtttttaga agagcagctt gttaaggcca aagaacagat tgaaaattac 720
aagaaacaga ccagaaatgg tctggggaag gatcatgaaa tcttgaggag gaggattgaa 780
aatggagcta aagagctctg gtttttccta cagagtgaat tgaagaaatt aaagaactta 840
gaaggaaatg aactccaaag acatgcagat gaatttcttt tggatttagg acatcatgaa 900
aggtctataa tgacggatct atactacctc agtcagacag atggagcagg tgattggcgg 960
gaaaaagagg ccaaagatct gacagaactg gttcagcgga gaataacata tcttcagaat 1020
cccaaggact gcagcaaagc caaaaagctg gtgtgtaata tcaacaaagg ctgtggctat 1080
ggctgtcagc tccatcatgt ggtctactgc ttcattgatt catatggcac ccagcgaaca 1140
ctcatcttgg aatctcagaa ttggcgctat gctactgggt gatgggagac tgtatttagg 1200
cctgtaagtg agacatgcac agacagatct ggcattctcca ctggacactg gtcagggtgaa 1260
gtgaaggaca aaaatgttca agtggtcgag cttcccattg tagacagtct tcatccccgt 1320
cctccatatt tacccttggc tgtaccagaa gacctcgag atcgacttgt acgagtgcac 1380
ggtgaccctg cagtgtgggt ggtgtctcag tttgtcaa atcttgatccg cccacagcct 1440
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gagtacatgg tgcattgtga agaacatttt cagcttcttg cacgcagaat gcaagtggac 1620
aaaaaaagag tgtatttggc cacagatgac ccttctttat taaaggaggc aaaaacaaag 1680
taccccaatt atgaatttat tagtgataac tctatttctt ggtcagctgg actgcacaat 1740
cgatacacag aaaattcact tcgtggagtg atcctggata tacattttct ctctcaggca 1800
gacttcctag tgtgtacttt ttcattccag gtctgtcgag ttgcttatga aattatgcaa 1860
acactacatc ctgatgcctc tgcaaacttc cattcttttag atgacatcta ctattttggg 1920
ggccagaatg cccacaatca aattgccatt tatgctcacc aaccccgaac tgcagatgaa 1980
attcccatgg aacctggaga tatcattggg gtggctggaa atcattggga tggctattct 2040
aaaggtgtca acaggaaatt gggaaggacg ggcctatatc cctcctacaa agttcgagag 2100
aagatagaaa cgggtcaagta cccacatat cctgaggctg agaaataaag ctcagatgga 2160
agagataaac gaccaaactc agttcgacca aactcagttc aaaccatttc agccaaactg 2220
tagatgaaga gggctctgat ctaacaaaat aaggttatat gagtagatac tctcagcacc 2280

```

253

```

aagagcagct gggaactgac ataggcttca attggtggaa ttcctcttta acaagggctg 2340
caatgccctc ataccccatgc acagtacaat aatgtactca catataacat gcaaacagggt 2400
tgttttctac tttgcccctt tcagtatgtc cccataagac aaacactgcc atattgtgta 2460
atttaagtga cacagacatt ttgtgtgaga cttaaaacat ggtgcctata tctgagagac 2520
ctgtgtgaac tattgagaag atcggaacag ctccttactc tgaggaagtt gattccttatt 2580
tgatgggtgg attgtgacca ctgaattcac tccagtcaac agattcagaa tgagaatgga 2640
cgtttggttt ttttttggtt ttgtttttgt tttttccttt ataagggtgt ctgttttttt 2700
ttttttaaat aattgcatca gttcattgac ctcattcatta ataagtgaag aatacatcag 2760
aaaataaaaat attcactctc cattagaaaa ttttgtaaaa caatgccatg aacaaattct 2820
ttagtactca atgtttctgg acattctctt tgataacaaa aaataaattt taaaaaggaa 2880
ttttgtaaaag tttctagaat tttatatcat tggatgatat gttgatcagc cttatgtgga 2940
agaactgtga taaaaagagg agcttttttag tttttcagct tatntacntt gttttttgtc 3000
cnggttc 3007

```

&lt;210&gt; 372

&lt;211&gt; 752

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (521)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 372

```

gttgacttgt actgaagggtg attttaaaatt taagtatgta gtgtttgaat ttcttccatc 60
catgtcggtt taatgagatg tttccatgtc agctccttta cagccttggc tccyggctta 120
cagatttttg aatagttggt tgcttgccag ttgttttaca tctttcattg gccacaaaaa 180
tattagccat ttgagatgag atgagactac ttgttgtacc ttcattcttc atttaatttt 240
ctggcgtaaa ttaacatttt aatttcatat atatctgtaa agagtctacc caaaggcttc 300
acggaaattt gcaaaatgaa ctaattccct ttttaagcagc aggtgtgcct gtttttgact 360
tttcagtaaa tatgttggtt gtgcacatat ctacatgggtg gagaccatat tcattatttc 420
atcttccaaa taatgggaaa aatataaaaag tgaatcagtg tgctttggga attcagtga 480
atcatgttaa ctcatataga gggggcctta gtttatctct nctttactga attaattagt 540
tttggaattt cttttaccat taaaaaaaat taaggaccat acagagaatg atttaagaaa 600
aaacaagtca cttaaaaatc atcacctatt tataaactgt attaattaca cataatgctt 660
attgattcaa tgaggtttct ctaaagactt ctgcttaata aatatggctg gacttcattt 720
aaattagttt aggactattg tagggatggg ag 752

```

&lt;210&gt; 373

&lt;211&gt; 712

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (11)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

254

&lt;222&gt; (560)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (638)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (682)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (683)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (708)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (711)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 373

```

gagagcctat ntcctagttt ctcccaatgt tatattttaat tttaaaaaat tgatatgaaa 60
atgtctaatag tatagtaata atttatgaca gatctagtca tttcttccta ttaaaaaaga 120
ttaccttatac tccagtagga aatggaattt tatgggcctt taaaagaaag ttttatgaaa 180
cttgatgcta taattttatt ggtatttcaa ggggaaaaaaa gcaactggggt tcaaaaatgg 240
tagcagaact gctttgaaat gctgcaaggt ggccactaga tgatgcaaaa tacaacccaaa 300
agattgactg agaataaaat taggtgacaa gggttttttaa agaataacct tttaaagtgt 360
gggggacaggg gttgcttttt tttattttat tttaaagtcaa ttatatttta catcttacat 420
ttctaaaagc attttataat tatttttagt aagatttttc ttaaaatttc atatactggt 480
ttctacaatt tatatttgaa atttctcagt gttatgtaaa gagtgatgga aaagcattga 540
tttcttttaa accgtaatgn ttttagaact taagcctata gggcctttct tacaatgggtg 600
atgtacccat tatcttagaa aatctagttt aaacctgntt tctttccccg caaaagaatt 660
aaatggggaa aatccatttg gnnatcctct taagttattc ctaattangt ng 712

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&lt;210&gt; 374

&lt;211&gt; 1807

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 374

```

ggcacgagtt atggattacc tagatatcgg tggcttactc atgcttgga tttttttcag 60
agagagttta agtgctgtgg agtagtatat ttcaactgact gggttggaat gacagagatg 120
gactggcccc cagattcctg ctgtgttaga gaattccccg gatgttccaa acaggcccac 180

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255

```

caggaagatc tcagtgcact ttatcaagag ggttggtgga agaaaatgta ttcctttttg 240
agaggaacca aacaactgca ggtgctgagg tttctgggaa tctccattgg ggtgacacaa 300
atcctggcca tgattctcac cttactctg ctctgggctc tgtattatga tagaaggag 360
cctgggacag accaaatgat gtccttgaag aatgacaact ctcagcacct gtcagtccc 420
tcagtagaac tggtgaaacc aagcctgtca agaactcttg aacacacatc catggcaaac 480
agctttaata cacactttga gatggaggag ttataaaaag aaatgtcaca gaagaaaacc 540
acaaacttgt tttattggac ttgtgaattt ttgagtacat actatgtgtt tcagaaatat 600
gtagaaataa aaatgttgcc ataaaataac acctaagcat atactattct atgctttaaa 660
atgaggatgg aaaagtttca tgtcataagt caccacctgg acaataattg atgcccttaa 720
aatgctgaag acagatgtca taccactgt gtagcctgtg tatgactttt actgaacaca 780
gttatgtttt gaggcagcat ggtttgatta gcatttccgc atccatgcaa acgagtcaca 840
tatggtggga ctggagccat agtaaagggt gatttacttc taccaactag tatataaagt 900
actaattaaa tgctaacata ggaagttaga aaataactaat aacttttatt actcagcgat 960
ctattcttct gatgctaaat aaattatata tcagaaaact ttcaatatgt gtgactacct 1020
aaatgtgatt tttgctggtt actaaaatat tcttaccact taaaagagca agctaacaca 1080
ttgtcttaag ctgatcaggg attttttcta tataagctctg tgtaaatact gtataattca 1140
gtcgatttca gttctgataa tgtaaagaat aaccattatg aaaaggaaaa tttgtcctgt 1200
atagcatcat tatttttagc ctttctgtt aataaagctt tactattctg tcctgggctt 1260
atattacaca tataactgtt atttaaatac ttaaccacta attttgaaaa ttaccagtgt 1320
gatacatagg aatcattatt cagaatgtag tctggtcttt aggaagtatt aataagaaaa 1380
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actctttttg acactaaaca ctttttaaaa agcttatctt tgccttctcc aaacaagaag 1500
caatagtctc caagtcaata taaattctac agaaaatagt gttctttttc tccagaaaaa 1560
tgcttgtag aatcattaaa acatgtgaca atttagagat tctttgtttt atttactga 1620
ttaatatact gtggcaaatt acacagatta ttaaattttt ttacaagagt atagtatatt 1680
tatgtgaaat gggaaaagtg cattttactg tattttgtgt attttgttta tttctcagaa 1740
tatggaaaaga aaattaaaaat gtgtcaataa atattttcta gagagtataa aaaaaaaaaa 1800
aaaaaaaaa

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&lt;210&gt; 375

&lt;211&gt; 1815

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (201)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 375

```

gagatcacc gctaccact gctcatcaga agtattctgg agaacacccc ggagagccat 60
gcagaccatt cctccctaaa gctggccctc gagcgggcag aggagctgtg ctctcaagt 120
aatgagggag ttcgggagaa ggaaaactcg gaccgactgg agtgatcca ggcgacgtg 180
cagtgtgaag gctcgcgga naacttattt tcaactctct caccaactgc ctggggcccc 240
ggaagctctt acacagtggg aaattatata agaccaagag caacaaggaa ctgcacggat 300
tcctcttcaa tgacttctg cttcttacct acatggtcaa gcagtgtgt gtttctctg 360
gctctgagaa acttttcagc tcgaagtcca atgctcaatt caaaatgtat aaaacgccc 420
tttctctgaa tgaagtcttg gtgaactgcc cacagaccct tccagcgatg agcctgtctt 480
ccacatttcc cacattgatc gggctctacac cctccgaaca gacaacatta atgagaggac 540
cacctgggtg cagaagatca aggcggcgctc tgagcagtac atcgacaccg agaagaagaa 600
gcgtgagaaa gcttaccagg cccgctccca aaagacttca ggcattgggc gcctgatggt 660

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## 256

```

gcatgtcatt gaagctacag aattaaaagc ctgcaaacca aatggaaaga gcaacccata 720
ctgtgaaatc agcatgggct cccagagcta caccaccagg accatccagg acacactcaa 780
tcccaagtgg aattttaact gccagttctt tattaaggat ctctaccaag acgtgctgtg 840
tctcaccttg tttgacagag accagttttc accagatgat ttcctgggtc gtactgaaat 900
tccagtggca aaaattcgaa cagaacagga aagcaaaggc cctatgaccc gccgactgct 960
gctgcatgag gtccccaccg gggagggtctg ggtccgtttt gacctgcagc tttttgagca 1020
aaaaactctc ctgtaggggt tctaaaggac agcaccagcg ggacagccca caaggctggg 1080
gctggagaat gagagactgc gctctcttgg ggctgaggga gcaccatgca gcttcacccc 1140
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tgcaaacacc tttcccataa agaaaccaa ccccatagta cagtgccttg tcctagtgtt 1260
cacatgttca gctctgtttg tttagatgcc aaggtttcca ttttcagggc tataaaaagt 1320
attacttgga aatgaggcat cagaccacca gatgttaccg ctcggttgaa tgtgtccacc 1380
gtggagtggg ttggtgacgc tgtaaccatt ccacgccagt gacctctgct gggtcacagc 1440
cactcaggag gggaagggtc aggatgagag ctgcagcctc gacacttgcg cggcctgata 1500
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ataaattatt tatgtaaatt cattgttttt gcataattct taggacatgc atctttaagc 1740
tttatcattg cccatatgta cagaaagaga ataaagacat atgtttatgg atggaamaaa 1800
aaaaaaaaaa aaaaaa 1815

```

&lt;210&gt; 376

&lt;211&gt; 550

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (483)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 376

```

gtatccccag gaggtcaaca ggggcttcat ttttctgagg gactagaggg tcttgtggag 60
ctcctgggac agagatctag atccagagag aacattcgtc cttccgatct cagctcagct 120
ctgagagccc tcccagagag cagctcccga gggctccaga gcctccgaaa gccctcccag 180
agagcagccc ccacctccca ggctgtctgc acttctcett gctatgcttt gctctgtaac 240
atTTTgcaac agtctgcagt acacgggggt tgTTaatctg agtattcatt gTTtctcttg 300
ctgggcagtg aacttgagga gggcagggat tttgtctgtt cactgctggr gyccagcac 360
ccaraatact taaatctgag ttggatgaat ggcggccagc cactgggatt ccagggttt 420
gggccccctg ccataacata tggcccargg cargcgccac atgctgggtc agtccccarc 480
ctnctgtyca caratccttc tctgttctac tccygggctg tkTccttcca cctcaactc 540
ggttctcagg 550

```

&lt;210&gt; 377

&lt;211&gt; 3202

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2957)



257

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (3119)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (3192)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 377

```

ctgctgaaga ccttgtgaga agatctgaga aagatactgc agctgttgtc tccagacagg 60
gcagctccct gaacctcttt gaagatgtgc agatcacaga accagaagct gagccagagt 120
ccaagtctga accgagacct ccaatttctt ctccgagggc tccccagacc agagctgtca 180
agccccgact tcatectgtg aagccaatga atgccacggc caccaagggt gctaactgca 240
gcttgggaaac tgccaccatc atcagtgaga acttgaacaa tgagggtcatg atgaagaaat 300
acagccccctc ggaccctgca tttgcatatg cgcagctgac ccacgatgag ctgattcagc 360
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gtttctgtga cttcactttc acctgctcca ggggtcaagg acttgccttg cctgataacc 600
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caatggaagc caggttaatg attacaatta atcttttact gtacattccc aaggctttag 720
ttttaaatgc cactgtgect ttaacaagggt tgtaaataatt ttatgccac cagagatgtg 780
gtcataagat ctgatcctga gccagagatt cagatggcac aggaagtatt catgtatttt 840
aacactgggg ttttctttct ttcatactga gatttttttt cagtatgtat cctccagctc 900
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aacagagggtg ttttagagaaa gcctctgagt atgcctttca gattttgaac aagcggcctt 1140
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cccttctact ggagatagga aaagttagaat tcaggaatta aaagaattac tctttattca 1260
atltgaggaa cttggtgaaa gcccctctc ttatgacagc caggttcctg ctggctagac 1320
cagcctatlc agcgttttgc taggggattg ggtggtccac gcactcgcta atacagttct 1380
ccagggtgtg aatgatgtca atacgattgc ttggcctttt cccctgtgct ctttgctcgg 1440
tgctctgggt tcctcagcaa cactccttgt aaggggcaga gacagggtcc accaactccc 1500
caagatgaag aagccccctc agggccagtcg tgggtggctca tgcctgtaat cccagcactt 1560
tgcaaggccg aggaggggtg atcacttgag gtcaggagtt cgagaccagc ctgaccaaca 1620
tggcgaaacc ccattctctac taaaaatata aaaattagct tggcatgggt gtgcgtgcct 1680
gtaatccag ctactcgga ggctggggca ggagaattgc ttgaacttgg gagatggagg 1740
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cttaaaaaaa gagcctgggc aattttttta agactctgtc ttaaaaaaaa ctaaaaagaa 1860
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tgaactgcat ctgcatgtct gtcttttgaa cactttctct ccctgcccac aaggaaaccc 1980
aaattatltg tgggatactg gggaaattgt agtgaagggc ttaatgtagt taataaaagt 2040
taaaagtcag tagaaaacag gtgcctcagc cttcaaattg ttgctttttt tccattttcc 2100
ctcatgaata gactcaccag cattttaccc ccttgttata aaactgtgca gagcaagaag 2160
atgatactta tttttgaatt tgtattttta aaactagatt tatagacttt tttttttttt 2220
aactagggca cttgcttctt tcttagctaa aagcaccagc tgagattttt caggtaattt 2280

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## 258

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tggtgttact cacttaagac tgggaattaga atgtttcttg tattttctcat ttttttccct 2340
ggctatgata gaatctcacc taatcttgac atctctccta ggggaagaat atcacaggct 2400
aatagcgtgg ttgggggtga agatgatagc agttattaaa tcaggaatct cttttatgta 2460
tgctcttggt acattgaggt taagagacaa aatcattggc agtgcaatct ctttccagga 2520
tttcgtttgc tgtggcattg gttatatcag agcactttaa tctgaaggat gatactgtaa 2580
cttgatttat ctaattagct ttttaattatc tacagctatt ttattttatt taattctctc 2640
ctacagtact gggaccactg taaactttctc agatgacttg tatttttgta gtgctatgaa 2700
atatttttac atacttataa agaaaactgt atgttcactt gaactctgaa aatgtacatg 2760
tatggctgga cgcggtggct cacgcctgta atcccagcac tttgggaggc tgaggcgggt 2820
gaatcacttg attgaggtca ggagttcgag accagcctgg ccaacatggc aaaaccccg 2880
ctctactaaa aaatacagaa attagctggg tgtgggtggc gacagctgta atctcagctg 2940
ctcgggaggc tgaggcncaa gaatcgcttg agccaggagg gtggagggtg cagtgcagctg 3000
agatcacatc attgcactcc agcctgggca acgggcgaga ctctgtctca aaaaaaagaa 3060
agaaagaaaa ggtacatgta tatatttgtc ctgcattatg ttttttactt gatataaang 3120
tatttttact gtgatagtca aaaaaaaaaa aaaaaaaaaa aactcgaggg ggggcccgg 3180
acccaattcg cncatagtg aa 3202

```

&lt;210&gt; 378

&lt;211&gt; 2401

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (179)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 378

```

aatatctcat gaatgagttt gaagtttgc tggattttga aatgaatggg actttgtctt 60
tattactaat tcaccaaatt tgttgagcgc aaaagcaatt aatgtagttt aagtatttag 120
tatgtacagt tctctgtggt aacagctgag aagtaagcaa ctttttctga ctgcataatg 180
gtgtattcct cttttgagtc ccataatat tttataaatt gtaatgccc atcttgtact 240
acagttgtct tattcgtatt gtttataaac tttgagggtt aggactgggt cttactcacc 300
tttatgtgcc ttccctatgc ttcaaagaat ttaccatcta atggaagaga acatttgcaa 360
gttggtccca taccaagctc cttccacata ctctactcat ctgaactttg aatgcagaat 420
ctttaaattg caaccccaca tactaaggctc aagaaagaac ttaatgggaa ttaatctcca 480
cccattagct ttaccctgac atcaggattg ccaaatecaa tggactcttg tctattctta 540
cgtgacttct gctggaaaat gcgaatgttg accatcctgc cacttggaac tctcttccca 600
ctcctcacat tgcttttgc accactggaa gttccttctg tttcttggg agtacctttt 660
gctgtctggg acttgtagat aatggtgttt cctagggtc cctccagggc cctctgctc 720
actaactgga tatacttttc ctgagcaaat ccaggaaac ttgcgtcaga ccgtgacttc 780
aaatacaggt tgataaatgc taaactgtct ccaaaccaga ctccatccta gcctccacac 840
ccagacaccc aactgctatg gatcaacttt ttagaatatc ctacttcaa actgacctta 900
cctaaaataa tgactttttc cccaataat tgccctgct atattcctta tttctgaatg 960
gtacctccta gctatataga ttatctgagg agcttactga aatgctgatt ctgaagataa 1020
ggggcatggc ttttaagattc tgtatttctg gcgagtacc aactgggtgct catgctgctg 1080
attgagaacc acttctgaat atagcaaggc tgtaaattat ccactacgtg ccctcgtaat 1140
tgtcttagtt caagcccaga ttattgtagt agacttagta tttctttgcc ttagttgatc 1200
tgtgacccct ccaatatcta ttccacactg ttgcctaagt ggccttagta aaattcaagt 1260
ctggttattt tattcccttg cttggaattt ctcaatgtag aatgaaactc attcagcatt 1320
aacacatagg cccttcttga tctgacatcg tgtttctcta gttagactaa agaatcccca 1380

```

259

```

ctatgaagtt gtttcatccg taagtacctt tgaaccacaga agcccccttt ctcatatggt 1440
tctcattcct gtttgcctt cagagttcag ctttagttgc taaaacattc agacatccct 1500
ctgacttaga tccccacta ctgtttttct gtgagaagca gctatgcata attcctcttc 1560
aacacagtag ttcttgaaat tttgcaggcc tctcctggaa aggaggaaat gacttctctg 1620
actttgtatg atgcttattt gtggatgaat gggcaaggga aaaaatgaag gaacaagtga 1680
atgaacagta tgggagtatg agaaaaggta taaattgggt atagttgaga aaaggattca 1740
aattgatctt tggttcgaga gacaatttca tctttctgat gaatttaaag tgtagtcttt 1800
gaaccagctg ggcttaatta tgtaaagttt tgagcctgag ataagcacac aatcacaaaa 1860
cctacccaaa caagtttttt gtttcacttc atctcttata aaacaatgtt ctaaagtaag 1920
tgatagggat gctcatcatt ctgctaccta ttatcacaaat gaaaacaatc ataaatagta 1980
cacaggaaag gtgagaaata gcggatagtt cttatttcat agtactgtat atggaaataa 2040
accaaatttg ctcatagaga tactatttta ttacctcaaa aatatataaa aatgaaaacg 2100
ttatgaaaat attttaaaat gggattttaa aataattgag aacatcacag caatttagaa 2160
tactaaagag catagcttta aaatgatagt gctgagaact cccacctct accccaccac 2220
ctgtaggctt ctttgacaac ttacaaatgt tctctagttt gtatctagaa tcacttatat 2280
ctttcaaata aaccaacttt gtgaacaaaa aaaaaaaaaa aaaagggcgg gccgctctag 2340
aggatccaag cttacgkaaa cgcgtgcatg cgacgtcata gctcttctat agtgtcacct 2400
a 2401

```

&lt;210&gt; 379

&lt;211&gt; 852

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 379

```

gccccagcgt cgacccacgc gtccgggtcg gtctcgctt gtcgccagct ccattttcct 60
ctctttctct tcccccttcc ttcgcgcca agagcgctc ccagcctcgt aggggtggtca 120
cggagccccct gcgccttttc cttgctcggg tcctgcgtcc gcgcctgccc cgccatgaat 180
gaggagtacg acgtgatcgt gctgggcacc ggcctgacgg aatgtatcct gtcaggata 240
atgtcagtga atggcaagaa agttcttcat atggatcgaa acccttacta cggaggagag 300
agtgcattca taacaccatt ggaagattta tacaaaagat ttaaaatacc aggatcacca 360
cccgagtcaa tggggagagg aagagactgg aatgttgact tgattcccaa gttccttatg 420
gctaattggtc agctgggtta gatgctgctt tatacagagg taactcgcta tctggatttt 480
aaagtgactg aaggagactt tgtctataag ggtggaaaaa tctacaaggt tcttccact 540
gaagcagaag ccctggcatc tagcctaata ggattgtttg aaaaacgtcg cttcaggaaa 600
ttcctagtgt atgttgccaa cttcgatgaa aaagatccaa gaacttttga aggcattgat 660
cctaagaaga ccacaatgcg agatgtgtat aagaaatttg atttggttca agacgttata 720
gattttactg gtcattgctt tgcactttac agaactgatg attacttaga tcaaccgtgt 780
tatgaaacca ttaatagaat taaactttac tactgtggaa agacaactgt ttaataaaaa 840
gatttacatt cc 852

```

&lt;210&gt; 380

&lt;211&gt; 2014

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 380

```

ggcatgttag tagacgactg aatatggaaa ggatatcgag ttatctattt tgttaatttt 60
atttttgttt tttatcatct agatttttat catggattag tctgaaattt aaagttcttg 120
ccagtcggtt ttctttcatt ttgtagtttt tacagtattt ccactgtgca tatgcaaaat 180
gggtattaca taactgtatc atatttggtt ttgataattt tttttttttt tgagacggag 240

```

260

```

tcttgctgtt gccaggctg gagtggagt cgtgggtgta tctcggctca ctgcaaactc 300
cgccctctgg gttcaagcga ttctcctggc ccagcctyct gagtagctgg gattacaggt 360
gtgtgccacc rtgccagct aatttttgtg tttttagtag agacgggggt tcaccatgtt 420
ggccggctgg tcttgaactc ctgacctcag gctatatgcc cacttccacc tcccaaagt 480
ctgggattac aggcattgagc cactgtgccc agcctgggtat tgataattta tattcagata 540
atttgttatg gctctttaat atcccacaag gggctctaaa aagcaaacat tcaagagtat 600
gtagttttta gacattaagt taattatttt aaacagtgcac agcaaaacac aagtgattaa 660
atatagttta tttgttccaa tgactaaatt ttacctcatt tattaatctg gtcattaagg 720
aatatattta ataattattat gtaattattc tttttatgca tgatacacct agaaaaatgc 780
cttttgtttc tattgatggc tttgttgttt ggagctactt ttgattactt attgcagttt 840
cccaatttag tctttacttt atctaactca caaagtaaaa ttaactgatc acatggcaac 900
tactgtattt aaatagttct ggaaaaatga aagtgtcttt tgctgcttgg taaatgggta 960
atgcccttga ttcccttgact gtaggacata gctgatctaa agtactctgt cagttttacc 1020
ttcacccatg actgtcatta gttgtcaaag ttgaaaagta ctttagctgt gagaaatcct 1080
tgtatgtttt tattataaga ggtataatca tctcaaagc ctgtttttat tacatgatgt 1140
ggactgatta ttttttctat cacagtgtta acagatggat tttattgtaa atacaaagaa 1200
aacatattga ttattgtagt attcttatgt cacctggcct tttgcgtgag attatttatt 1260
atttctagca aggcctttctt cctttcttat tgcccagaga ctgactgata catcttttgt 1320
tatttttaca cataaattaa acatagcctt tttggacaaa ttcactaaat attaattgat 1380
aaaatgtaat tgagtaaatt tttatcagaa ttttaaaaat aaaagagctt agactcagta 1440
gaactcagta gaagcttcac tatttactcc agcgtgtgta aattgtactt actctattct 1500
cagagtatat ttaactgtct taccattgat tctttccctt tgctaatttt ttttttgtt 1560
aatggtagct ggcactttag gtgggggtata ttttcttctc ctaagagaat agacagtttt 1620
tccagattca tcatcattga ctgtcaagaa aggaccttc agcaaggctg taccctcaat 1680
gcagttgatg gcctgtcttc acggatttac agacttggcc tgatgcccac gtaaatcaaa 1740
gctttggctt gtggtacaaa ccacaagaag acaagcatct gtggtgcgga ggcaagcagg 1800
ctaactagga gttgacaagc taagaaagtg aaactgttct ttcttagtta actgtctttc 1860
tctggagctc tgttattttg agtataatat ttccacgaca cttagtaaat gcaagctaaa 1920
atgtaataat aataaattgt attggagaaa cctaaaaaaa aaaaaaaaaa aaaaaaaaaa 1980
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaa 2014

```

&lt;210&gt; 381

&lt;211&gt; 565

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (557)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 381

```

nggggtgggg ggccctaatt gagaggtgtg ggtttsgcra gaaaraaaga aaattcccca 60
cttggaaga aagaggagga aactggatt ctwactttct ggatcttrac actgggctgc 120
aaaacctacc ttctctctc ccgcctcccc tcacctcaa ctctcaatgt cttgctgtca 180
ttttctgtct cggctccctc ctcccccttc ccccttcccc caccacacac ccttcacct 240

```

## 261

```

ctgtgtcctg gtccttctga gggccactgc agatgactct cctttgaaat gagaaaaaga 300
aaagaaagca agaacagaaa acgaagccac aggaaggga gtagacattg tatgcttatg 360
gtttctcatt atgaagggtgc agcttgtagg aggtttgtac ggatgtgctt tgaagttatg 420
tatattacat ataacaggaa aaaatattaa aataaacagt gctggtaagt atgaagctga 480
cattctaaaa ttataattat ctgactgtga ttgatgtatc ctgaggttcc tagatcttac 540
tgaactggcc cagcttngga gacct                                     565

```

&lt;210&gt; 382

&lt;211&gt; 131

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 382

```

gtcgacccac gcgtccgccc acgcgtccgc ccacgcgtcc gcccacgcgt ccgaaaaaaaa 60
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 120
aaggcgccg g                                     131

```

&lt;210&gt; 383

&lt;211&gt; 2026

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2026)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 383

```

gggcgcgcgg cctcgaggcc ttccggtgcg ggagaaacta ctactcccat aatgccccgc 60
ggtcccggag cttgccagtc tcgtcgcgag aagcagcggc ccggggcgac tgagcggaca 120
aacggaagtg taggttacgg tctgagacat caccgccaag ctgggcatcg gggagatggc 180
cgagactgac cccaagaccg tgcaggacct cacctcgggtg gtgcagacac tcctgcagca 240
gatgcaagat aaatttcaga ccatgtctga ccagatcatt gggagaattg atgatatgag 300
tagtcgcatt gatgatctgg aaaagaatat cgcggacctc atgacacagg ctgggggtgga 360
agaactggaa agtgaaaaca agatacctgc cagcaaaaag agttgaagg tgcataaat 420
ttatactgga atctggcatt tttccaagcc aagagaagat cgaatggctt tttgcagcta 480
actactatgt gtagacagg tttatattat aaagtatgca ttcttatcac ctagtatata 540
gttagtttgt agagtgattt cccccagtt tcttgaacat ggtatcttca catcttgga 600
cttggtcagt tgtgctattc attattaaac actaaaactt tggcggttct tgcataacat 660
tgtcagattt tttagtgtat ttctgtgaag tcattttttt tcttgctatt cctttttag 720
tagttgctgt ttggataaaa gttgatgtgt gattttttat taaacaaata gtaaaccctt 780
caattatagt tagtcttggg gaagtaagat gttttagtag ttttagagttc ttttaattctt 840
ggcacaacgt gactgttgag ctaacaccaa atagtgtgtt ggcaatactt ttcaaatggc 900
tgaaaacacc taaaaattgt tcattcagaa atatctgtca ctgctctgtt gccaaaactc 960
agaatagaac ttagacgtat gtctgagtc ctgagatcac atgctaaagt cgatgaaaag 1020
taaccactgc cactgtcttg tgcagaact tttacagtac agaaaataac agaatagcct 1080
tctgtaatga ggcgtttgtt agagttttgc atgagattct aatacttcag taggacccta 1140
cctacgtggg tcatctacaa tggttaccat aaaaaatctg gcaggatttt aaaactcaat 1200
cagtctttcc tttgagctag tgacttgaaa agaaagagag aaggaaaaga gaccatatta 1260
agtccatgcc agttgcttgg ctagaatatg atcaacgact tgtagtagac tcaagttttt 1320
aaaaaacact attttactta aactgtttct tatctaaatt cttgcagagt gtcaatgtta 1380

```

262

```

tcattgatta tagaagacag ggataataacc tttatctctg gccactcaaa aatgcagtgc 1440
caggagtgct aaacctagag gcccaatactg atgacctgga aggtgatcca tatgattgtc 1500
accacaaagt gcttttacac aaaaacttga aaatttgaaa aacatgattt ttttaagttt 1560
ctcatctcac cagtcttggt rtttatattg caaatctatc aaagtaagaa ataatttgtg 1620
ctgtatacaa attacatggg gaacataaag gagtgagatc cttctgtgat aaaatgaatt 1680
caccactctg gttacccaac tacagaacct cctttgatca ggccagtagg ttgtgatgca 1740
ggctggagcc cccgaatgcc ccacacacac tgcagcattg accagaccat ccgaaacctg 1800
cgcccttggg gatgttctca agcctcggaa gtggcaaatg gaaatgatat ggccggttgc 1860
ggttgtagga gagttgtgac ttaggcagga gtcgacctcc tcaagtaatg gaacgatttc 1920
aaaggcaggc tgccctgacc aaaaatatct gccatgaata aaggtgcctg aaatcctgct 1980
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaan 2026

```

&lt;210&gt; 384

&lt;211&gt; 1346

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (249)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (251)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1334)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1342)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 384

```

tcgaccacgc gtccgcgcgc gcggcgggcg cgaggcgaag aaggaggagt gtgtgcggcg 60
gggcccgcgc ggtaaaggcg agaaggctgc aggagaccga gggggagccg ggccggtggg 120
gccgccgcgc ccgccatgca ggaaatcatc gccagcgtgg accacatcaa gtttgacttg 180
gagatcgcgg tggagcagca gctgggggcg cagccmctkc cscrgcagac acagcctcca 240
gcaaagcana naaccccgca ggtcatcggg gtcatgcaga gtcaaaacag cagcgcgggc 300
aaccgggggc cccggccact ggagcaggtc acctgttaca agtgtggcga gaaaggacac 360
tacgccaaac gatgcaccaa agggcacttg gcctttctca gtggacagtg acagcagctg 420
gagccagctc cgagcagccc gggggcccg ctgttgggag tgtgcattta actgtttcat 480
gcgcttgttg gcgcgactgt ggctcgagct ggcccgcaga cacgtgggtt tcatcactct 540
gagggggccac gtctgttagt ttccatcat tttgccttag tattttttga aaaagggaca 600
tgtgtcctgt gggtccttgc agtcgacatc atgtttggct gggcatcgat gcctccttcc 660
tgggactccc ggcacaactc cctcatcca gggagggagg cagctgctgg ggaggggctt 720
ggctaggtag ttctgtgtgg cggtgggtcat tccccctatt aaacaccagt tcttgggtgac 780

```

## 263

```

gccaggggct ggtagggtcat tcaaagctgt ggccagctca cgcctgcttc ctcctccct 840
gccctgctga atcctaaagc tgtgcctata tctgtgattt gaatgagga gccctttggg 900
gcaaattcag gtgcccccat tgcctcaggc tggccctggg cccaggtggc agcggttgag 960
gaggggtaca gggctctcaa gcctgaggtt ttcttctctg ggcttaattt tctcttggg 1020
tacgtgcctg acagtgttta aggtgtccgt tgaactggag ttgcagactt ttaaatagat 1080
gacccttca gatcatctgt gcctacctcc tgcccatcag gcgtctacac tgtcactcag 1140
acacctgtgg catgtggagg agactgccct gtcctgagcc tggaaaatgt gaaactgtct 1200
cctgcaacct gctgggcatg tgggcctggc tgtgttcaat tgcaagaaca atttttatga 1260
aatggattaa agcttgtttt ttaaaaaaaaa aaaaaaaaaa ytcggggggg gscctgtacc 1320
cattggccct tggngggggg tnttaa 1346

```

&lt;210&gt; 385

&lt;211&gt; 637

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (637)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 385

```

gcccacgcgt tcgcccacgc gtccgcccac gcgtccgaat ttcacgtttt tatgtaagca 60
tgaaacacag gcagtatgag agaaagcaag gccggtcatg ctgtccgtac actacgtatg 120
ctgtagagcc attttgtatg ttgtgtaaaa caaaaagcat tgatgaaaaa gcaaaagggtg 180
atgtatgtat atgagaaaaa taattgtacg atatcattcc agtacgtttt gttgtacatt 240
ttagtcttgt ttactttctc ttcattgtta agaggatgcg aactgtacag tttccagcta 300
gttaccata ttagagaaga aataagagag tattagaaga aaacaggaga gaaagaacat 360
ttgtgaattg cagttgtcaa aaaaaaaaaa tagcctagct ggccttattt gtgaagcata 420
attgctttta gcatatggaa gtattttttc acattttctt tgtataaaat ttgtattaaa 480
cttaaatatc tttttgatgg tgggtgtttct ttgtgactga gccagtagac tcacactata 540
tgcttttttg gggttgcccg ttccttcccc cccccccca gttttttcag atttytttac 600
ctttttttta ttaaactgtt ttggaaaaaa aaaaaan 637

```

&lt;210&gt; 386

&lt;211&gt; 862

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (723)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (760)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

264

&lt;222&gt; (780)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (809)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 386

```
gggggcagttg ccgcgggcgcg cgcgatccgg ctgacgcacg tggccccggt tccccaagac 60
cagagcgggg ccgggagggg gggggaagag gcgagagcgc ggagggcgcg cgtgcgcatt 120
ggcgcgggga ggagcagggg tcttggcagc gggcgaggag gctgcgagcg agccgcgaac 180
cgagcggggc gcgggcgcgc gcacatggg ggagaaacc gggaccagct caccgtgtac 240
ttgggcaagc gggacttcgt agatcacctg gacaaagtgg accctgtaga tggcgtgggtg 300
cttggtggacc ctgactacct gaaggaccgc aaagtgtttg tgaccctcac ctgcgccttc 360
cgctatggcc gtgaagacct ggatgtgctg ggcttgtcct tccgcaaaga cctgttcac 420
gccacctacc aggccttccc cccggtgccc aacccacccc ggccccccac ccgcctgear 480
gaccggctgc tgaggaagct gggccagcat gcccacccct tcttcttcac cataccccag 540
aatcttccat gctccgtcac actgcagcca ggcccagagg atacaggaaa ggctgcggs 600
gtrgactttg agwtcgagcc ttctgtrcta aatcactaga agagaaaagc cacaaaagga 660
actctgtgcg gctggtgatc cgaaagtgc ttcgccccgg agaaaaccgg gcccagctt 720
tanccgaaaa caaaaggcat tccttcattg ctgaacggtn cctggaactt cgaaggtttn 780
ccttgaaaaa aggagctgta cttaccatng gggagcccct tcaatggtaa aatgttccaa 840
gttaacaaaa aaaatttcaa cc 862
```

&lt;210&gt; 387

&lt;211&gt; 585

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (375)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (474)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (573)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 387

```
gctgcaaaaca aaaagaatga agctcgactg agaattgtaa aaactcttga agacattgat 60
ctgggcccta ctgaaaaatg tgtgagagtc aactcagttt ccagtgggtct ggcggaagaa 120
gacctagaga cctttttgca atcccgggtc ctctcttcca gcctgatgct accaaagggtg 180
gaaagtctcg aagaaatcca gtggtttgca gacaaatttt cattccactt aaaaggccga 240
aaacttgaac aaccaatgaa tttaatccct tttgtggaaa ctgcaatggg tttgctcaat 300
```



## 265

```

tttaaggcag tgtgtgaaga aaccctgaag gtcgggcctc aagtaggtct ctttctagat 360
gcagtcgttt ttggnaggag aagactttcg agccagcata ggtgcaacaa gtagtaaaga 420
aaccctggga tattctytac gcccggcaaa agwttkttgt catagcgaaa cctnttgggt 480
ctccaagccg tagatctggg tgtacattga ctttcgagat gggagctggg gcttgcttag 540
gacagttcac ggaggaaggg agccgccatg ggnttttcac tgggt 585

```

&lt;210&gt; 388

&lt;211&gt; 591

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 388

```

gtgatctgca tgtggcaggg ctgcgcagtg gagcggccag tgggcaggat gacgagccag 60
acccctctgc cccagtcgcc cgggccaggg cgcccgacga tgtctactgt tgtggagctg 120
aacgtcgggg gtgagttcca caccaccacc ctgggtaccc tgaggaagtt tccgggctca 180
aagctggcag agatgtttct tagcttagcc aaggcctcca cggacgcgga gggccgcttc 240
ttcatcgacc gccccagcac ctatttcaga cccatcctgg actacctgcg cactgggcaa 300
gtgcccacac agcacatccc tgaagtgtac cgtgaggctc agttctacga aatcaagcct 360
ttggtcaagc tgctggagga catgccacag atctttgggtg agcaggtgtc tcggaagcag 420
tttttgctgc aagtgccggg ctacagcgag aacctggagc tcatggtgcg cctggcacgt 480
gcagaagcca taacagcacg gaaktccagc gtgyttgtgt gcctggtkga aactgaggag 540
caggatgcat attattcaga ggtcctgtgt ttttcttgca ggataagaag g 591

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&lt;210&gt; 389

&lt;211&gt; 1096

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 389

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ggcagagcaa gatgggggct taccacacca tcgagctgga gccaaccgc cagttcaccc 60
tgccaagaa gcagtgggat agtgtggtac tggagcgcac cgagcaggcc tgtraccag 120
cctggagcgc tgatgtggcg gctgtggtca tgcaggaagg cctcgcccat atctgcttag 180
tcactcccag catgaccctc actcggggcca aggtggagggt gaacatccct aggaaaagga 240
aaggcaattg ctctcagcat gaccgggccc tggagcgggt ctatgaacag gtggtccagg 300
ctatccagcg ccacatacac tttgatgttg taaagtgcac cctggtggcc agcccaggat 360
ttgtgaggga gcagttctgc gactacatgt ttcaacaagc agtgaagacc gacaacaaac 420
tgctcctgga aaaccggtcc aaatttcttc aggtacatgc ctctccgga cacaagtact 480
ccctgaaaga ggccctttgt gaccctactg tggctagccg cctttcagac actaaagctg 540
ctggggaagt caaagccttg gatgacttct ataaaatgtt acagcatgaa ccggatcgag 600
ctttctatgg actcaagcag gtggagaagg ccaatgaagc catggcaatt gacacattgc 660
tcatcagcga tgagctcttc aggcacacag atgtagccac acggagccgg tatgtgaggc 720
tggtggacag tgtgaaagag aatgcaggca ccgttaggat attctctagt cttcacgttt 780
ctggggaaca gctcagccag ttgactgggg tagctgccat tctccgcttc cctgttcccg 840
aactttctga ccaagagggt gattccagtt ctgaagagga ttaatgattg aaacttaaaa 900
ttgagacaat cttgtgtttc ctaaactgtt acagtacatt tctcagcatc cttgtgacag 960
aaagctgcaa gaakggcact ttttgattca tacagggatt tcttatgtct ttggctacac 1020
tagatatatt gtgattggca agacatgtat ttaaacaata aactaaaagg aaataatcwm 1080
mamrtaaaaa aaatgc 1096

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&lt;210&gt; 390

&lt;211&gt; 448

266

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (76)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (132)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (394)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (439)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (447)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 390

```

tcggaggacg cgaaccggca cgctgcgcct ttaaggagtc cggctgggct gggcgccgga 60
gctgggagcc gcgcgngtag gagcccggcg caggggccca gcccggggct agagaccgag 120
ggccgggggtc cnggcccggc ggcggggaccc aggcgggtga ggctggtcag gagtcagcca 180
gcctgaaaga gcaggatgga tcttgatgtg gttaacatgt ttgtgattgc gggcgggcacg 240
tggccatccc aatcctggca tttgtggctt catttcttct gtggccttca gcactgataa 300
gaatctatta ttggtactgg cggaggacat tgggcatgca agtccgctat gttcaccatg 360
aagactatca gttctgttat tccttcgggg gcangcctgg gcamaaamcc tccatcctca 420
tgctccacgg attctcttnc cacaagnt                                     448

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&lt;210&gt; 391

&lt;211&gt; 1451

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (17)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (18)

267

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1429)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1440)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 391

```
gtcgacccac gcgtcenncc acgggtccggt ggggagaagc cgggaggact ggggtgcgcct 60
gcagggatcg gaagccgggt ggggtgtgag aggttttctc gctctaggga gattcttcaa 120
gcaatcacta tgtcaacaga cacagggtgt tcccttcctt catatgagga agatcaggga 180
tcaaaactca ttcgaaaagc taaagaggca ccattcgtac ccgttggaat agcgggtttt 240
gcagcaattg ttgcatatgg attatataaa ctgaagagca ggggaaatac taaaatgtcc 300
attcatctga tccacatgcg tgtggcagcc caaggctttg ttgtaggagc aatgactgtt 360
ggtatgggct attccatgta tcgggaattc tgggcaaaac ctaagcctta gaagaagaga 420
tgctgtcttg gtcttgttgg aggagcttgc tttagttaga tgtcttatta ttaaagttac 480
ctattattgt tggaaataaa ctaatttgta tgggtttaga tggtaacatg gcattttgaa 540
tattggcttc ctttcttgca ggcttgattt gcttggtgac cgaattacta gtgactagt 600
tactaactag gtcattcaag gaagtcaagt taacttaaac atgtcaccta aatgcacttg 660
atgggtgttg aatgtccacc ttcttaaatt ttaagatga acttagttct aaagaagata 720
acaggccaat cctgaaggta ctccctgttt gctgcagaat gtcagatatt ttggatgttg 780
cataagagtc ctatttgccc cagttaattc aacttttgtc tgcctgtttt gtggactggc 840
tggtctctgt agaactctgt ccaaaaagtg catggaatat aacttgtaaa gcttcccaca 900
attgacaata tatatgcatg tgtttaaacc aaatccagaa agcttaaaca atagagctgc 960
ataatagtat ttattaaaga atcacaactg taaacatgag aataacttaa ggattctagt 1020
ttagtTTTTT gtaattgcaa atttatattt tgctgctgat atattagaat aattttttaa 1080
tgtcatcttg aaatagaaat atgtatttta agcactcacg caaaggtaaa tgaacacgtt 1140
ttaaagtgtg gtgttgctaa ttttttccat aagaattgta aacattgaac tgaacaaatt 1200
acctataatg gatttggtta atgacttatg agcaagctgg tttggccaga cagtataccc 1260
aaacttttat ataataataca gaaggctatc acacttgtga aattctcttg tctaacttga 1320
atttgcattc catggtgtta acatggtata tgtattgtta ttaaagtaag tgacccatgt 1380
caaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaana aaaaaaaaaa 1440
aaaaaaaaa a 1451
```

&lt;210&gt; 392

&lt;211&gt; 1425

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (48)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

268

&lt;222&gt; (1332)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1381)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 392

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agttaataag taaaagctac taacaattaa aaaataaata aataaagnca agactgtctg 60
gaaaatggct ctctataaag gaccagttgc catcatccac agtggaagat tcaaagcagt 120
tggtccttgg tacgtatgag aagcggattt cattcccttg aattctacag agcagtttat 180
tagagtgaat gcattttaag gccttgcat t gatatgtca tccagttcat aatcaagttg 240
cctttttctg gctaaaacat aatgattatg tttttttctc atttggctct acaagctgct 300
ggccctttgt ccctccactg tgggaatcag atctagagca ggctgagcct gcagacacag 360
cagtggccaa aaggctactc taagtgtttt gtcttgactc cttacttgaa gtccaccag 420
ctagcacaca tctggtttat actgaagccc cctgcctaga aatactcatt tcaggaacca 480
ccagtaagca tctgtgacca cacaggcttt ttgactgatg gcttcccgga tctggtttca 540
agggataacc ccgtctgtgt gcatctatgg tcttctctct acagcgagga ctttgagtg 600
ctgcttggtg tccacacaag gggctcagag ctgagctctga actgcttcat ggccaccagc 660
tcctgtccct tccagtcttg agaggctttt ttctccagat ggaacctttc cttcccgcgc 720
ttttctcggt ctctggctgt ttttctcttg tgcccgctc attggacacc tcctggcttc 780
catctctgtg gttctcctgc ctacttctt gttctgttgt ttttccggtt tgtcaaaata 840
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aatctgttga ctaactccag gctcactcag gctcacctgc ctgctctctg caccagcctt 1140
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cagtgtttat tgtaacgcca aaccaacaaa tcacaggtgc ttgcttctct ccataaatct 1320
caacagtcta antttttgtc attcaacatg actcgtttat ccaacctgaa atcgcatata 1380
nccgcaaata tgggtgttagg gacttccgta gaagttccct tagat 1425

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&lt;210&gt; 393

&lt;211&gt; 4755

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (124)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2562)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 393

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agcggcgcc agtggaacca catgcttggc tacctggcgg cgctggccaa ggctgcttc 60

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269

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ggcggcaaca tcgagctctt cgtcttcttc aacggcgcg ctcgagaaagg cccggctgca 120
cgantgggtc aagcggcagg gcaacgagcg ccaracggca cagcagatcg tmagccatgt 180
ccagaacaag ggcaccccg cgcctaaagg ctggttcctg ccgcccgtyt gcatggccca 240
ctgcatccgc ctggcgctca tccgcttcca cgtcaagggt gcacagagca ttgaggatca 300
ccatcaggaa gtgattgggt tctgcagaga gaatgggttc catggcttgg ttgcgtatga 360
ctctgattat gcactgtgca acatccccct ctatttcagt gcccattgccc taaaactgag 420
ccggaacggg aaaagtctca ccacaagcca atatctgatg catgaagttg ccaagcaact 480
ggacctgaat ccaaactcgt ttcctatctt tgctgctctc ttaggaaatc acattctgcc 540
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atgagggcct tcttgccctg catgaggtcg gacaccccag ccatgctcaa ccctgccaac 1920
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cagctatcag ctctcttcat gagtggagta gacatggcct tgtttgcaaa tgatgcatgc 2160
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acgggtgacg ccaggggccc cagccactct gaaagtgcct tgaataatga ctctaaaacg 3060
tgcaatacaa atcctcattt aaatgcacta agtacagaca gcgcttgccg cagagaagct 3120

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270

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gctctggagg cagctgtcct aaataaagaa gagtaaactt attttttata gaggggtgaag 3180
gatgctggaa gggtaaggat ttaggaatat ctggagagaa agagagcctg cagttatgta 3240
cattttgtcc ttccgtaag agaaaaatga ggactttgga aattcagatc cctctttgat 3300
atcagagatt taaacaacac atttttagtt ttaaccagtt gtagtcaaaa tgctacaata 3360
aaacaaaaaa gagaaagaaa atgaagagca tttgactccc gcacttaaaa tgaagtacac 3420
ataaagttta aactggttat gacaaaagcc tatagtgtgt tttcttgaa cataaagaaa 3480
acaaattttg gcagtcttta agtatatata gcttaaaata taatttttag catttggcac 3540
catatgtatg ccattatatt tgattttgca ttactgtttc acaatgaagc tttctttaag 3600
gctttgattt ttatgattat gaaagaaata aggcacacc acagtttttc tttcttaaat 3660
ttcatcactg ttgatgtggt tcttttgtgt taaaaaaaaa aagtgcact atcaaaacta 3720
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ctttacaagc aagttaaatg gagataaagt tgaaatcata gaagatgcaa atgacctttc 3840
aaaatcaaca caatgtgttc tgaaactttc gtgactaata ccatgcatct gtgatcaatg 3900
aactatgtgg ttttgaatcg gatgtagacc attagtacta ctacttgagc taaactttctg 3960
catggttcat aattttttaa gtgtgtagtt aatatgcatg ttatcgtcct tcttccatt 4020
cttaacagta tgtgccatt tgcaaaacaa aaatgctaata atcagtaata agtcctataa 4080
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caacattacc ctggtgtatt cactgctgta tgcattattg ttctttgttg ctgttttatg 4260
ccttcatatt agcaaatatg aaattctgtg aaaaaaaacc ctttgatctt aaaaaaaaaa 4320
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ctgctgttg gtttgattga ctgtcgatgg attgtggtgt ggtgtatctg aaggctattg 4680
aatgcaactt acaatgctta ataaaaatct ttattctttt agtataaaaa aaaaaaaaaa 4740
aaaaaaaaaa aaaaaa 4755

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&lt;210&gt; 394

&lt;211&gt; 3039

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 394

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aaaccgaaa gttttagga aaattgctgc acatggcctt tgcagaaaag agagccttca 60
aaacctctta cattccagta gaaaactctc tctgcaagtc cttacttttg ttcactcatt 120
ccaggaagg gcttcaatat tggatattca cacagagccc agtttttcaa gtttgctttc 180
acagtcacg tatgctgaca tgggtgttcc acttcctgca aaaaacttaa tatttaaaga 240
tggtgtctta tcagaatgga gtggacggtc accttcctca cttcttattg ctaatctcca 300
tttgcaataa tttggttaca ccatttgttg ctcacacttt ctgccttttt tctttcttaa 360
cgtagcttt atagtgtcag ccactaaaaa gcacctgtct gctgcagtgc aattcttgct 420
taactaatat taaaagttgg ggaacatatt catgttttct gaagttttgc tcattattgc 480
acatcttatt gcgacaaagt gcttttttagc agccagcact gtatttttta ccttgagaca 540
atctgcattt cttttataaa actaagtata tactttatag gctttatgat gactgttatg 600
tttataagca gtcactatga aaattgcaat ggtaatttta tatgttagtt tatcaaacat 660
aatctttgtt taattttata ttttgttacc tatactttgg gggatcaagg gaagagatgg 720
aactcttct ctgaaaaggc ttcttggtac ttaaagtagt aaaactataa aacaataaac 780
atccagtatt gagagatgat atgataggc attatgaatt cctatgggtg tctgtaaatt 840
atgtatgtca gttggacatt gtagaaggta tgtaaatcag catagtgtgt tataacttaa 900
ccttgattta taaggctcta agattatgac tattcattga catctcatga gaagctttag 960

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271

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aagactttct atttttaaac accatttata tgtggacttc tgttgtcact gactttgggc 1020
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tttcttgagt cattgattct ttttagcatct caaatgttaa ttagaataat tggaatcact 1380
tttttagactt ttcaagttac cttccttggg aagtttgtgc agtgttatag tttagtttag 1440
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acataataca tgtwtacaaa taaamtgtgg tawtgatca 3039

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&lt;210&gt; 395

&lt;211&gt; 3276

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (3258)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (3260)

&lt;223&gt; n equals a,t,g, or c

272

<220>  
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 <223> n equals a,t,g, or c

<220>  
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 <222> (3263)  
 <223> n equals a,t,g, or c

<220>  
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 <222> (3270)  
 <223> n equals a,t,g, or c

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 gggaagaaat cagactgctg tgagagaaga gatgwtctc ctggcaaact acttgatag 180  
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 ttttgggtgga actgcaggaa tggcatttgt gggaacagtg tgttcaagga gccacgcagg 420  
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273

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tttacgaccc cggtctcnan gnnaaacctn ttttat 3276

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&lt;210&gt; 396

&lt;211&gt; 1632

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 396

```

ggcagagtgg aagagggggcc ttatgtgaat gattgccaca tactgtttct gttgctgctt 60
tttttccgat tcttttttgt cattggattt gtttgttttg tcatgtgggtg aatgggtgtt 120
tagttattgt gttgctgcc gaatcagaat ccagttcttg ttcttactgc cttatagtta 180
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gatccttgga ttttaaagga agagtatgtg ctttgaaggc actcagagac tagtaatagc 660
atatggtttg aagggaaacc cattctcttt caattacaag agagcatcac ttagcgtgca 720
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tctaataatat atcatatatt tcaggcttct atttgaaaac aggtataaga gatgatatga 1440

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274

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tacaacccta tagataatgt tttttgcttg attgacttat ataatcactg tttcatgatt 1500
actgcttttg gaataatagg aagttttgtg aaatgctggc cttgtgtata tcttagaattg 1560
caaatttaat aaagtgtgta tacatgcata aaaaaaaaaa aaacctcggc cgcgaccacg 1620
ctaagccgaa tt 1632
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&lt;210&gt; 397

&lt;211&gt; 808

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 397

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ctgcaggaat tcggcacgag gtgtcatgaa tagaaacttc caaatgtaac catggaagct 120
aagtttggcc tgctttgctt tttagtctcc acaccatggg cagaactgct gtctttacta 180
cttcactctca cccaagtccc gttcccaggc agccaggggc ctgggtttga ataattgcag 240
ggccagcctg ccatgatctt tctcacttac tctctccca ttcagcaatc aaccagacta 300
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gaaaataaaa gtttctaaat ttacattttt atagggtatt gtaaataaaa acaaattgta 780
tacttaaaaa aaaaaaaaaa aaaaaaaaaa 808
```

&lt;210&gt; 398

&lt;211&gt; 2428

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1025)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 398

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ctgaatgcca tcgggttcaa gaagaaaatg ctaggcttaa gaagaaaaaa gagcagttgc 120
agcaggaaat cgaagactgg agtaaattac atgctgagct cagtgaagca atcaaatcat 180
ttgagaagtc tcagaaagat ttggaagtag ctcttactca caaggatgat aatattaatg 240
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aaaataaagg tggaaatgat tcagatgaat tagcaaatgg agaagtggga ggtgaccgga 360
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tatcggtagt tgaagaggat ctaaagcttt tacagcttaa gctaagagcc tccgtgtcca 480
ctaaatgtaa cctggaagac caggtaaaga aattggaaga tgaccgcaac tcaactacaag 540
ctgccaagac tggactggaa gatgaatgca aaaccttgag gcagaaagtg gagattctga 600
atgagctcta tcagcagaag gagatggctt tgcaaaagaa actgagtcaa gaagagtatg 660
aacggcaaga aagagagcac aggcgtgtcag ctgcagatga aaaggcagtt tcggctgcag 720
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agcgggtcatt taaaaaccag atcgctaccc atgagaagaa agctcatgaa aactggctca 840
```

275

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aagctcgtgc tgcagaaaga gctatagctg aagagaaaag ggaagctgcc aattttragac 900
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cgtcacctgt ggaactctac aagtgatt
2428

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&lt;210&gt; 399

&lt;211&gt; 2732

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (699)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 399

```

gtgtaaatat gccttatact tctgctggaa acagctaaca gacagggtaa taatagccta 60
ggttccccca aagtactgta caagaagata agttatattc acctagcggg aaaaaaagt 120
ggctaaacta gctccagaga acttgtgaat tctttgctaa aggctctttg ttttaggcat 180
ttgatgaagc aattgctgaa ttggatacgc tgaatgaaga gtcttataaa gacagcactc 240
tgrtcatgca gttacttagg gacaatctca ctgtaagtac tacttccaca gggtttatag 300
tctctttcct attcacctac ttaataattc actgttatct tcaagagggg atttgtacca 360
ttaaatgtag ttacagtttt aagttgttaa atttgttata aatgactgct gaagttttga 420
cctttgcaat catccctatc tgcagtgaca caggaataat tttaaactgt cgagtgagat 480
aagattatac atactgggcc acttacctag ggaactttta gtagccctgc tttgattata 540
cttcccttct cttgcagctg tggacatcgg aaaaccaggg agacgaagga gacgctgggg 600
agggagagaa ctaatgtttc tcgtgctttg tgatctgttc agtgtcactc tgtaccctca 660
acatatatcc cttgtgcgat aaaaaaaaaa aaaaaaana gaatcgtacg tcgactttcg 720

```

276

```

atattttcaca gcctcagcct aggaaaaaatg gttcatggga taaacagctg gtattttgtat 780
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aaaaaagggc cgctcgcgat ctgactagt cc 2732

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&lt;210&gt; 400

&lt;211&gt; 1362

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1175)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1250)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

277

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 <222> (1263)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1285)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1343)  
 <223> n equals a,t,g, or c

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 ctttgatgt tttaccagtc aaaggtectc agggttctcc tcttctctca cgggcggctc 180  
 gccctccgga tcagctggcc tccgaagagc cgtggactgt cctacccgag cacttgattc 240  
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 ctgtgagggt actgagattt gagctgtgct ggccagcgca ttgcctcaca gtcacgcgcg 360  
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 tatccacaaa acagtcaatg ttcccgtgga gtgggtttgat ctatatacac tgtgacgatg 480  
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 <211> 1403  
 <212> DNA  
 <213> Homo sapiens

<400> 401  
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 aaaagaaata attttatttt tcccccttgg ggagatatta tcctctaata tgagaatcag 240  
 atccctagat tctattttct cctatactat taaactcaac cttgaacctg agcttggttg 300  
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278

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&lt;210&gt; 402

&lt;211&gt; 2387

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1257)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1316)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 402

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279

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&lt;210&gt; 403

&lt;211&gt; 4062

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (111)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (4061)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 403

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280

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281

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&lt;210&gt; 404

&lt;211&gt; 861

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (11)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (25)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (734)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (746)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (767)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (769)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (820)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (849)

282

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (854)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 404

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&lt;210&gt; 405

&lt;211&gt; 1030

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 405

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&lt;210&gt; 406

&lt;211&gt; 2428

283

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 406

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&lt;210&gt; 407

&lt;211&gt; 2047

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

284

<400> 407  
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aaaaaaaaa 2047

&lt;210&gt; 408

&lt;211&gt; 892

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (21)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (33)

&lt;223&gt; n equals a,t,g, or c

285

<220>  
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<222> (855)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (868)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (891)  
<223> n equals a,t,g, or c

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<210> 409  
<211> 696  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (675)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (676)  
<223> n equals a,t,g, or c

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## 286

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tatagatcat ggatataaag agatacctga tttttattaa aaagatactt tttcaaattt 300
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atataraaac tatannaaaa aaacaaaccc gggatt 696

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&lt;210&gt; 410

&lt;211&gt; 1885

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (741)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 410

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287

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cgatcccaca gcctcaaaaa aaaaa 1885

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<210> 411  
 <211> 584  
 <212> DNA  
 <213> Homo sapiens

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<400> 411
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<210> 412  
 <211> 1412  
 <212> DNA  
 <213> Homo sapiens

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<400> 412
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288

<210> 413  
<211> 364  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (363)  
<223> n equals a,t,g, or c

<400> 413  
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ccnt 364

<210> 414  
<211> 1333  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (1140)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1196)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1210)  
<223> n equals a,t,g, or c

<220>  
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<222> (1246)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1285)  
<223> n equals a,t,g, or c

<220>



289

<221> misc feature  
 <222> (1287)  
 <223> n equals a,t,g, or c

<220>  
 <221> misc feature  
 <222> (1306)  
 <223> n equals a,t,g, or c

<400> 414  
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<210> 415  
 <211> 3146  
 <212> DNA  
 <213> Homo sapiens

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## 290

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tacactggac atgaaaacaa agactgggtt agcagcagac attgggtttac tctgcagcct 1920
gtgttttctg tttccccctt tcccacctcc tttccccccac ccaatccttt ttttttctt 1980
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agagtgcagg ctaggctgtc ttgggggaaat aaacattaaa acttaaagca aaaaaaaaaa 3120
aaaaaaaaactc gagggggggc ccgtac 3146

```

&lt;210&gt; 416

&lt;211&gt; 594

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 416

```

acatacgaaa tttgacaggt attgtatacc ctttggatct ttaggaatta atttttgcct 60
ctgtcactca gctttgtata ttttgaaatg gagataagta tagggagggtc ttggaaggaa 120

```

## 291

```

aattgccaga attcccaaac catgtaacac tcattgagaa ttccagatcc attatatcta 180
aagggcaagt gaaggaaaca gtattgtgaa ctgggtataa ctcccttggtt cttacttagt 240
acattcttaa tctgtgagac ccaaagggtg ataaacaata atttaagatt gtacagtact 300
ctaaacgtct gcaaagggtc agatgttatc agtatcacta gtttttattt ctgccagtag 360
ctccctttta ggttacattg ttgtcctctt tccagtgts gcatctgtcat tggtttttca 420
ctatggcaag ttcattaaaa agcttgctcc attgttatct tcaagtaatg cccataagga 480
gatggaagat atctgagaca attaaggctt tagcttctag gcaagagaaa taacgttgca 540
ttaaatttca agtttctttc tgctagactt gaatgtgtct agccactcta attt 594

```

```

<210> 417
<211> 562
<212> DNA
<213> Homo sapiens

```

```

<400> 417
gggaagggtt ccaagcctct aaaaatgtgc tttgtgatca ggagtgcgct ccaaaccaaa 60
tacgcgcgct gccctttcga ggccagttag ctcagcctcc aaggctttaa agccacattt 120
cagcaagaga aagcgtctgag agctcgcagg ttcatataag aaggcaaagc actggtttct 180
ctccttagaa aagtaggttt cttggcttga ttagactagg cttgctttga tttttagtga 240
agggaatgta cgtaaaacaa aatagggtct ggctgggtcaa aggagacaag caggatggat 300
ggatggatgg atggatggat gtatggatga atagatagat ggtgtttgca tgtaaattgc 360
agagaaaaca aaaccaaaagc tgattggaaa caattaattg tgggtgtctg agggggaagg 420
tcgcagcttt gggcagcttt gagaagcggg acaagagttc tgtgcctgtg tgtccagccc 480
tggagccagc cagtgcattt attttaagct cttagaagca actccttggc ccaggaatgc 540
gtgaccctg agatgggtcc ac 562

```

```

<210> 418
<211> 1412
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (1218)
<223> n equals a,t,g, or c

```

```

<400> 418
gggggagccc gcggtgctg ggagctgcgg cgctggccct ggggggagcc ctggggctgt 60
accacacggc gcggtggcac ctgcgcgccc aggacctcca cgcagagcgc tcagccgcgc 120
agctctccct gtccagccgc ctgcagctga ccctgtacca gtacaagacg tgctccctct 180
gcagcaaggc ccgagccttc ctgcacttcc atgccctgcc ctaccagggtg gtggagggtga 240
accctgtgcg cagggtctgag atcaagttct cctcctacag aaaggtgccc atcctggtgg 300
cccaggaagg agaaagctcg caacaactaa atgactcctc tgtcatcacc agcgccttca 360
agacctacct ggtgtcgggg cagcccctgg aagagatcat cacctactac ccagccatga 420
aggctgtgaa cgagcagggc aaggaggtga ccgagttcgg caataagtac tggctcatgc 480
tcaacgagaa ggaggccag caagtgtatg gtgggaagga ggccaggacg gaggagatga 540
agtggcgcca gtggcgggac gactggctgg tgcacctgat ctcccccaat gtgtaccgca 600
cgcccaccga ggctctggcg tcctttgact acattgtccg cgagggcaag ttcggagccg 660
tggaggggtg cggtggccaa tacatgggtg cagcgcccat gtacctcacc agcaagcgac 720
tcaagagcag gcaaccgctc caggacaacg tgcgcgagga cctctatgag gctgttgaca 780
agtgggtggc tgctgtgggc aaggaccggc ccttcatggg gggccagaag ccgaatctcg 840

```

292

```

ctgatttggc ggtgtatggc gtgctgcgtg tgatggaggg gctggatgca ttcgatgacc 900
tgatgcagca cacgcacatc cagccctggg acctgcsggg ggagagggcc atcaccgagg 960
ctccccagcg cactgaatgt cccccgcgca gagcagaggg aaggcaagcg gaagacgcca 1020
gctgccccaa gcttggggcca ctggggccag cgcctggcga tactggttgg gggcaggatc 1080
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cccacccctg ggttccccctg gttcccactc ttcccaagcc tcccgggact gggacatggt 1380
tgcaataaag gaaagggttg tggcgccaaa aa 1412

```

&lt;210&gt; 419

&lt;211&gt; 1939

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1872)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1884)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1889)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1924)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1929)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 419

```

gagaagacga cagaaggggg cgcctctctc agtggtagcg cgggggactgg ctgggaagcg 60
gtcggctcgag tgtggcctgt gtggactcgc atcttgcccc aagccggggcg gaggagagct 120
caagctaagg gtgatcagcc catgacctaa acctccagac aaaataaaac ggaaaatttg 180
ctagaatcaa gaatgatgga tccatgttca gttggagtcc agcttcgtac tacaaatgag 240
tgccataaaa cctactatac tcgtcacaca ggttttaaga ctttgcaaga attgtcatca 300
aatgatatgc ttttacttca acttagaact ggaatgacac tttctgggaa caatacaatt 360
tgctttcatc atgtaaaaat ttacattgac agatttgagg atttacagaa gtcattgtgt 420
gacccattta acatacacia gaaattagcc aaaaaaaatt tgcattgtaatt tgacttagat 480
gatgccactt ttctgagtgc taaatttgga agacagcttg tacctgggtt gaagctttgt 540

```